Recent Developments in γ-Lactone Synthesis

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Abstract: In recent years, several classes of biologically active molecules containing the γ-lactone ring, pesticides, plant and fungal growth inhibitors, and antibiotics have been found. Thus the synthesis of substituted dihydrofuran-2(3H) ones is a continuously developing area. Few general synthetic approaches to their stereoselective synthesis with broad structural variety are known. This article reviews the latest developments in the synthesis of γ-butyrolactones. We focus on the ring-closing steps and pay special attention to how different authors obtain the correspondent 4-hydroxycarbonyl compound; an acyclic synthon for the γ-lactone ring.

1. INTRODUCTION

γ-Lactones are widely distributed in nature; this moiety is present in around 10% of all natural compounds. Most display a broad biological profile including strong antibiotic, antihelmetic, antifungal, antitumour, antiviral, anti-inflammatory and cytostatic properties which make them interesting lead structures for new drugs [1]. Given their widespread occurrence in nature and their broad range of biological activity, a great deal of attention has been paid to the synthesis of this ring (for example, see some of the most recent reviews [1-3]).

In many cases, an αmethylene group in the lactone ring, which is potentially able to blind the nucleophilic sites of biomolecules by conjugate addition, manifests its own biological activity [4]. To avoid this review from becoming too lengthy, we have excluded the synthesis of α- or γ-methylene-γ-lactones and butenolides (Fig. **1**), which deserve a review of their own.

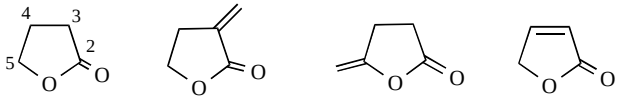


Fig. (1). More common hydrofurans derivatives in natural products.

2. γ-LACTONES FROM RING TRANSFORMATION

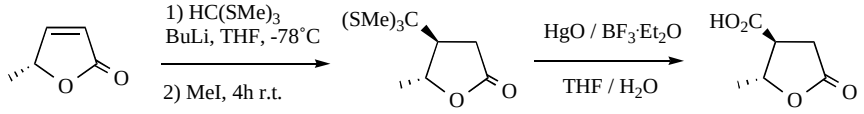
This review, with recent developments in the synthesis of γ-lactones, will focus on ring-closing methods. However, we will begin with some methodologies based on the transformation of five already built member rings.

The synthesis of γ-lactones from butenolides by catalytic hydrogenation is a common method. Quiral catalysts for enatioselective hydrogenation have been the focal point of most research works conducted in recent years [5-10]. 3-Halo or 3-phenylselenyl butyrolactones can be reduced by nickel chloride/sodium borohydrides to lead to the removal of the halide or phenylselenyl group [11].

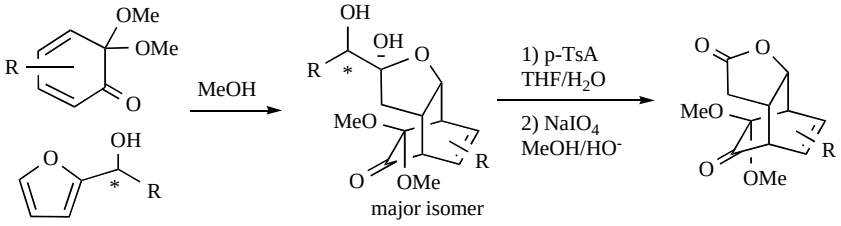
Brückner *et al.* [12] described a new application to the synthesis of 4-carboxy-γ-lactones from butenolides by employing Li-$C(SMe)_3$ and MeI to obtain the 4-[tris(methylsulfonyl)methyl] derivative which, under a Lewis acid-assisted hydrolisis with Hg (II), led to the carboxy group (Scheme **1**). In all cases, a *trans* selectivity was observed with very high yields (>90%).

On the one hand, γ-Lactones can be obtained from succinic anhidrides by reduction with $NaBH_4$ or Li(*t*-BuO)$_3$AlH, but the regioselectivity of the process cannot be controlled [13,14].

On the other hand, Yoshimitsu *et al.* [15] described an oxidation process to obtain γ-Lactones from tetrahydrofuran derivatives.



Scheme 1. f 4-carboxy-γ-lactones.



Scheme 2. Diels-Alder cycloaddtion-oxidation tandem in the synthesis of γ-lactones from furans.

Therefore, this is a review of the new or improved methods developed in the last ten years for constructing γ-lactone rings.

They used ruthenium tetroxide under modified Sharpless conditions to obtain moderate results. The oxidation of γ-lactols is also a usual procedure for γ-lactones and one of continuous use [16].

Diastereoselective Diels-Alder cycloadditions of masked *o*-benzoquinones with furans (either racemic or homochiral) lead to highly functionalized tricyclic heterocycles which can be transformed into tricyclic γ-lactones by oxidation with $NaIO_4$ (Scheme **2**). High yields are described in all cases [17].

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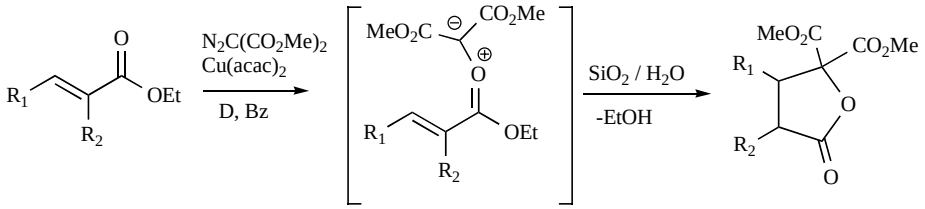
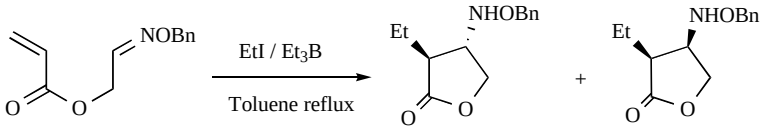


Scheme 3. γ-lactones via 1,5-Electrocyclic ring closure.



Scheme 4. Tandem radical addition-cyclization of oxime ethers.

3. γ-LACTONES FROM C-C BOND CYCLIZATION

Two main synthetic approaches can be found in the literature for the synthesis of the γ-lactone ring: cyclization by either C-C or C-O bond generation. Although the latter is more common, some methods relying on C-C bond formation can be emphasized.

Only two references have been found for C4-C5 bond generation in the cyclization process. 1,5-Electrocyclic ring closure reaction of carbonyl ylides from conjugated esters and diazo bis (carbonyl) compounds offers an easy and highly efficient method for the preparation of polyfunctionalized γ-lactones (Scheme **3**) [18]. Michael addition of chiral dioxolanones to α,β-unsaturated methyl esters gives 3,4-disubstituted-γ-lactones with high enantiomeric excess [19].

The remaining references concerning C-C bond generation focus on the formation of the C3-C4 bond.

Naito *et al*. [20,21] applied a novel tandem radical addition-cyclization of oxime ethers and hydrazones that are intramolecularly connected with an α,β-unsaturated carbonyl group (Scheme **4**). A diastereoselective study was described. These authors described a similar procedure by sulfanyl radical addition-cyclization of dienes connected with hydroximates [22]. γ-lactones were effectively derived from hydroximates by either hydrolysis or oxidation. This method was successfully applied to the practical synthesis of (±)-oxo-parabenzlactone. Similarly another example was the Cu(I)-catalyzed intramolecular [2+2] photocycloaddition of 1,6-dienes in which two alkane units were ethered through acetal oxygen [23]. The resulting bicyclic lactols were then oxidized to γ-lactones by Jones reagent in a moderate overall yield.

Anionic or radical cyclizations from synthons A (Fig. **2**) have already been described. Unsaturated malonyl esters underwent Pd-catalyzed intramolecular allylic alkylation to give 4-vinyl-γ-lactones [24]. The reaction could be achieved with a substrate by incorporating a judiciously positioned silicon moiety (Z=$SiEt_3$). β-Ketoesters successfully provided fused cyclopropane-γ-lactones by Mn(III)-mediated oxidative cyclization [25,26]. These cyclopropane-γ-lactones were also accessible from allyl diazoacetates with some copper (I) or dirhodium (II) catalysts [27,28]. The Grubbs catalyst can be used for a metathesis cyclization process in the synthesis of Rollicosin [29], and to also promote atom transfer radical cyclization from trichloroacetic esters derivatives [30]. Martín *et al*. [31,32] described a base-induced cyclization of enantiomerically-enriched α-[(phenylthio)acyloxy]-α,β–unsaturated esters to obtain highly substituted butyrolactones with a high degree of sterocontrol. α,α-Difluorinated-γ-lactones are accessible via their corresponding lactols, and likewise, with a highly steroselective radical cyclization promoted by tributyltinhydride [33].

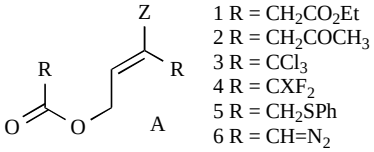


Fig. (2). Different synthons for anionic or radical cyclizations.

Bromoallylicacetals give lactols in the same way with a highly stereoselective radical cyclization [34]. In both cases, oxidation to γ-lactones is performed by traditional processes. Mehta *et al.* [35] developed a synthesis of xanthonoid natural products via tandem Wessely oxidation-intramolecular [4 + 2] cycloaddition. They used α,β-unsaturated esters from an oxidate aromatic system with the Diels-Alder cyclization protocol to lead to tricyclic lactones. As a final example in this group, we have included a Lewis acid-promoted cyclization of heteroatom-substituted enynes to obtain halogenated y-lactones. Cyclized products are highly substituted by the silyl and phosphonate groups, and are suitable for further elaboration [36].

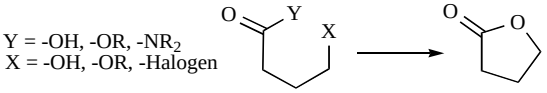
4. γ-LACTONES BY C-O BOND CYCLIZATION

Most of the methods for the synthesis of γ-lactones use this synthetic approach.

These procedures can be subclassified in accordance with the acyclic building block required to build the adequate number of atoms for ring generation. Thus, γ-lactones are cyclized by the C-O bond formation either from a C4 building block or after a previous generation of the C4-C5, C3-C4 or C2-C3 bond. This chapter is arranged accordingly.

4.1. γ-Lactones by C-O Bond Cyclization from a C4 Building Block

The most common method for γ-lactone rings from a preformed hydrocarbonated chain starts from an acid derivative with an X group in the γ-position (Scheme **5**). In the last ten years, some applications of this methodology have been published. Cyclization from γ-hydroxyacids by acid [37-40] or enzimatic [41] treatment was used for the synthesis of several natural products.

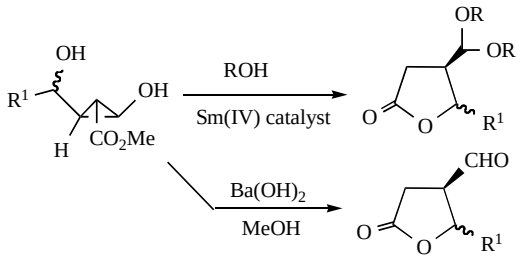


Scheme 5. General procedure for cyclization by C-O bond formation from a C4 building block.

Recently, this methodology has been applied: with O-chiral protected derivatives to obtain pure enantiomeric products [42,43], and in synthesis of natural products [44-46]. Three approaches are referenced from γ-haloacids: from α-brominated benzoic acids the cyclation was optimized by using CsF-Celite as a solid base giving good yields [47], from γ-iodoacids in fluorinated substrates it was optimized by aqueous sodium carbonate [48] or triethylamine [49].

Similarly, some references for the cyclization step from γ-hydroxyesteres or γ-hydroxy-protected groups in acid medium are found either in solution [50-61] or in solid-phase [62] synthesis. Most of these papers focus on studies into the stereoselective build of synthons to perform the cyclization process. All the efforts centre on obtaining chiral γ-lactones which have an important biological activity.

Reiser *et al*. [63-66] developed an interesting methodology for γ-lactones cyclization based on a retro aldol-lactonization sequence from a cyclopropane synthon (Scheme **6**). This methodology was applied to the synthesis of several natural products and obtained excellent results.



Scheme 6. Retroaldol/lactonization cascade.

Satoh *et al.* [67-72] developed a lactonization process from γ-chloro esters in acid medium. These substrates were obtained from optically active 1-chlorovinyl-*p*-tolyl sulfoxide by conjugate addition of a lithium enolate. Good yields and an elevated enantiomeric excess were found, and an exhaustive study was presented.

Several authors have used epoxyesters as substrates for lactonization. α,β-Epoxyesters were treated with thiophenol to afford α-phenylsulfonyltrisubstituted-γ-butirolactones. A diastereoselective study about the epoxidation process and cyclization are shown [73,74]. β,γ-Epoxiesters were used by Concellón *et al*. [75] in an intramolecular ring opening of the epoxide with the carboxylate group ($Me_3SiCl/NaI/\Delta$) at the most favoured position, leading to β-hydroxy-γ-butirolactones with moderate yields (58-60%). β,γ-Epoxiesters were recently used for the synthesis of γ–lactones by the tandem epoxide opening-cyclization reaction mediated by samarium (II) diiodide with excellent yields [76]. γ,δ-Epoxiacids are cyclised to γ-lactones by acid treatment: $HClO_4$ [77], BF_3-Et_2O [78] or $ZnCl_2$ [79]. In the last paper, a study on the stereochemistry control is shown. The regiochemistry of the reaction is governed by the *cis* or *trans* nature of the starting epoxyacids, whereas a mechanistic hypothesis involving an oxocarbenium ion as a common intermediate is presented in the interpretation of the results.

Amides, as acid derivatives, are also used as starting materials for the cyclization process. Some new applications have been developed from the γ-hydroxy- or the γ-hydroxy-protected group and are especially described for obtaining enantiomeric γ-lactones [60, 80-82]. We can emphasize the oxazolinyl group [83], isoxazolidine [84], β-lactones [85] and morpholinones [86,87] as protected versions of precursors of the target lactones. The enantioselective results indicate that these are very efficient methods.

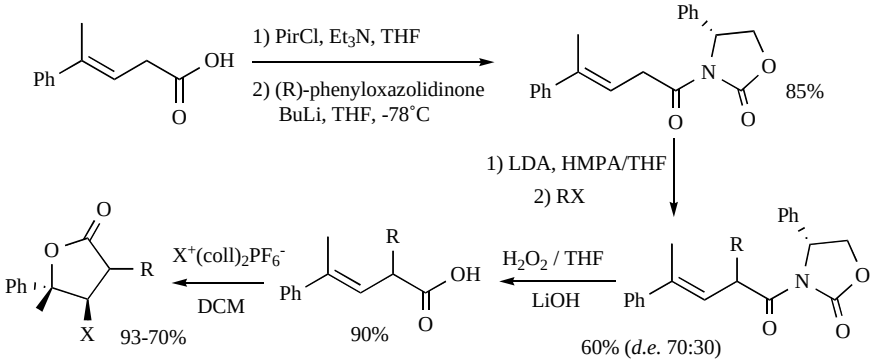
As usual, γ-hydroxynitriles can give γ-lactones by hydrolysis in an aqueous base followed by acidification. This was applied to the synthesis of (*R*)-4-hexanolide [88]. In a similar way, *o*-alkylaromatic carboxylic acids can be converted into γ-lactones in a single step by using $NaBrO_3/NaHSO_3$ [89]. This reagent generates HOBr which delivers a Br-radical in the aqueous solution to give the brominated benzyl group which undergoes an intramolecular nucleophilic attack in the same medium.

Khan *et al*. [90] synthesized γ-lactone-fused cyclopentanoids from tricyclic α-ketohemiacetals through the α-haloester functionality upon cleavage of the bond between the carbonyl and hydroxy group. Cleavage reaction conditions using $Pb(OAc)_4$ or alkaline hydrogen peroxide gave good results.

Another approach to the synthesis of γ-lactones from a C4 building block is the use of a γ,δ-unsaturated acid as the starting material with acid treatment, which is another methodology used [91]. In some cases, no lactonization was obtained under such conditions. Miura *et al*. reported that a silyl group at position 5 plays a crucial role in accelerating acid-catalyzed cyclization [92]. The difference in the geometry of the carbon-carbon double bond did not affect the reaction rate.

Other authors have described the conversion of unsaturated acids to γ-lactones catalyzed by a treatment with DTSA/$HClO_4$ in an isomerization-lactonization process [93]. Angelici *et al*. used the solid sulfanic acid catalysts Amberlyst-15 and Nafion SAC-13 for the same process [94]. The π-Allylmolybdenum complex from γ,δ-unsaturated carboxylic acids may also be the starting material to afford γ-lactones via the demetalation process. A diastereoselective study is included [95].

One of the most efficient methods for the cyclization to γ-lactones is the halolactonization process, which is continuously applied [96-101], including via solid-phase conditions [102]. We emphasizse a new preparation of 3,5,5-trialkyl-γ-butyrolactones of a defined absolute configuration [103]. This method involves: diastereoselective alkylation of 3,4-ethylenic acids after incorporating Evan's chiral auxiliary, separation of the two diastereoisomers, hydrolysis of the auxiliary and stereospecific halolactonization (Scheme **7**).

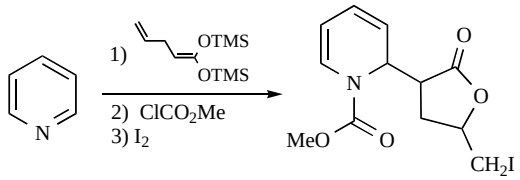


Scheme 7. Alkylation-halolactonization sequence.

A mild and convenient method for polyfluoroalkylation use either sodium bisulfite or sodium sulfite to initiate the reaction of polyfluoroalkyl iodides with 4-pentenoic acids [104-109]. A radical addition to the double bond is proposed to obtain 4-iodo-5-polyfluoroalkyl derivatives which are cyclized to γ-lactones in the same step.

Tunge *et al.* [110] demonstrated that diphenyl diselenide is an efficient catalyst for the halolactonization of unsaturated acids. Hydroxy selenenylation followed by ring closure was also studied [111,112]. The scope and limitations of this methodology are described. Both electronic effects and the nature of the substituents are critical in the stereolectivity of the reaction.

A special halolactonization was developed by Rudler *et al.* [113-116] which used bis(trimethylsilyl)ketene acetals with pyridines, quinolines, isoquinolines or pyrazines as starting materials (Scheme **8**). γ-lactones were obtained in a one-pot reaction with iodine or bromide treatment. The regio and diastereoselectivities of the addition reactions, together with the presence or absence of rotamers, were established.



Scheme 8. Bis(trimethylsilyl)ketene acetals in the synthesis of lactones.

A different approach to γ-lactones from β,γ– or γ,δ-unsaturated acids is via symmetric dihydroxylation and cyclization [117-119], or via hydroxylation from a quiral oxazolidinone [120]. Important natural products are directly accessible in this way. An alternative route to obtain the hydroxyl group was developed by Evans *et al.* [121] from a reductive ozonolysis of the allylic system.

Interestingly, a mild and efficient synthesis of fused tricyclic γ-lactones mediated by manganese (III) and copper (II) was developed by Burton *et al.* (Scheme **9**). Very good yields were described and a radical oxidative cyclization was proposed [122].

Another oxidative process with electrochemically-generated hypervalent iodine and β-phenylpropionic acids was developed by Nishiyama *et al.* this year [123].

Alkylidene Meldrum's acids have shown a direct entry into vinyl-substituted γ-lactones by Pd-catalyzed intramolecular allylation with high stereocontrol [124]. A similar approach with hydroxy-Meldrum's acid derivatives was described previously [125].

One method which is always effective for γ-lactones cyclization is the reduction of γ-ketoacids or γ-ketoacid with $NaBH_4$ or derivatives [126-130]. Another reduction process may also be used, such as catalytic hydrogenation [131,132], selectride [133], SmI_2 [134] or enzymatic reduction [135].

$PhSCF_2SiMe$ has been demostrated as a difluoromethyl carbanion synthon, which reacts with γ-ketoesters in the presence of a catalytic amount of TBAF to the γ-hydroxyalkylated product that undergoes cyclization in the same medium [136]. Some stereoselective studies in this area have been developed [137-139]. The free radical additions of fluorine-containing halides to 4-pentenamides in the presence of $Na_2S_2O_4$ have also been studied [140].

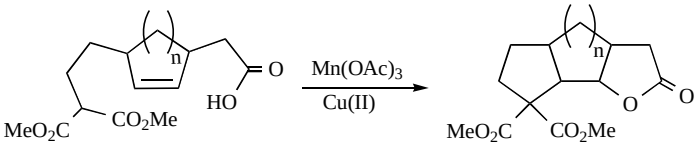
A soluble ruthenium carbonyl hydride cluster is able to catalyze the hydrogenation of a succinic acid to a γ-hydroxyacid followed by ring closure in a one-step reaction with quantitative yields [141].

γ-Lactones are also accessible by a simple oxidation process from lactol acetals [142-147], or from free or protected 1,4-diols [148-152]. The most usual oxidants are Jones reagent, TPAP, PCC or $NaIO_4$, but in some cases, ruthenium catalyst [153,154], TEMPO/NCS/R_4NI [155,156] or the enzymatic process [157] are used. 4-Hydroxyvinyl carbamates may undergo epoxidation, rearrangement and oxidation of γ-lactols as a new stereoselective synthesis of bicyclic γ-lactones. Previous access to vinyl carbamates from asymmetric homoaldol reactions offered high enantioselective products [158,159]. More specific oxidation reagents were used either from 4-nitro alcohols [160], 4-keto-1,5-diols in tricyclic derivatives to obtain diquinane-based symmetric bis- γ-lactones [161] or 1-hydroxy-protected-4-en olefines, which were cleavaged to carboxylic acid by RuO_4 [162].

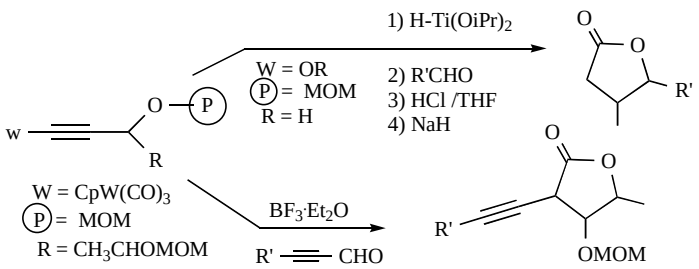
A new strategy to transform bicyclic and tricyclic β-lactones to δ-hydroxy-α,β-ketophosphonates into fused γ-lactones via a Wolff rearrangement/cyclization [163], or by a rhodium (II)-catalyzed O-H insertion process [164], has been developed.

Two different approaches of the hydroxyalkynyl systems have been developed in recent years (Scheme **10**). Sato *et al.* [165] used 3-alkoxy-2-propyn-1-ylcarbonates to generate alkoxyallenes, such as the homoenolate equivalent, which reacts with aldehydes to yield γ-lactones. Liu *et al.* [166,167] used the alkenylation of MOM derivatives by chiral alkynyl tunsteng species with alkynylaldehydes and $BF_3{\cdot}Et_2O$ as the key step. This method provides an easy entry into (-)-Litsenolide and (+)-Isodihydromahubanolide A.

Cyclopentenones can be transformed into γ-lactones by the chiral $Ti(O\text{-}iPr)_4$/tartaric ester t-BuOOH complex in an oxidative process to produce moderate yields. Indeed, the process is highly enantioselective (93-99% e.e.) [168].



Scheme 9. Fused tricyclic γ-lactones mediated by manganase (III) acetate.

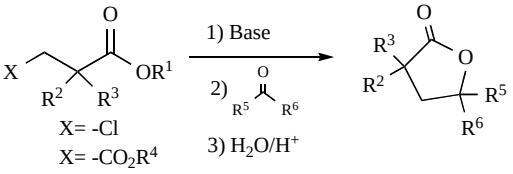


Scheme 10. Approach to γ-lactones from hydroxyalkynyl systems.

The last procedure in this group is that described by Kita *et al.* [169] and Iida *et al.* [170]. They developed a mild and clear direct oxidative C-H lactonization of both aliphatic carboxylic and benzoic acids based on a selective benzylic C-H abstraction strategy, leading to biologically important aryl lactones, by using a combination of hypervalent iodine (III) reagents with KBr.

4.2. γ-Lactones by C-O Cyclization after C4-C5 Bond Formation

As we have just seen, in most cases it is necessary to have an X group at the γ-position (C5) to complete the cyclization to γ-lactones. The nucleophilic attack of a suitable substrate to a carbonyl group leads to a hydroxyl group at this position. Different kinds of esters can be deprotonated or lithiated at the β-position to their carbonyl group. The carbanion formed can react with different aldehydes and ketones and will produce several γ-lactones (Scheme **11**).



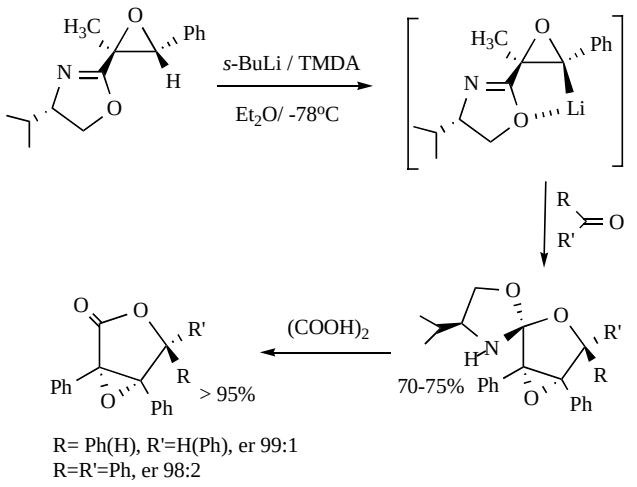
Scheme 11. γ-Lactones from β-deprotonated esters.

Pohmakotr *et al.* showed that the vicinal dianions derived from α-arylsuccinic esters react with carbonyl compounds in a regioselective way at the β-carbon in the presence of $ZnCl_2$ to furnish α-aryl-γ-butyrolactones with moderate yields [171,172].

Starting with β-lithiopropionate derivatives, Yus and Pastor obtained the expected 3,5 or 5-substituted-γ-butyrolactones by a reaction with different aldehydes and 5,5-disubstituted ones either by a reaction with ketones [173] or using a lithiated orto-ester [174, 175].

By using a β,γ-epoxyester, deprotonation takes place in a stereoselective manner to provide the corresponding oxiranyl "remote" anion. The generation and reactions of these novel anions were developed by Thebtaranonth *et al.* [176,177]. These authors concluded that the anions formed were stabilised by chelation between the lithium and carbonyl moiety ester. These oxiranyl anions underwent a consecutive aldol-lactonization reaction with adehydes to provide the corresponding epoxilactones.

Prior to lithium-ester chelation and stabilization, Florio *et al.* found that β-aryl oxazolinyloxiranes were stereospecify β-lithiated thanks to intramolecular chelation. The trapping reaction of such



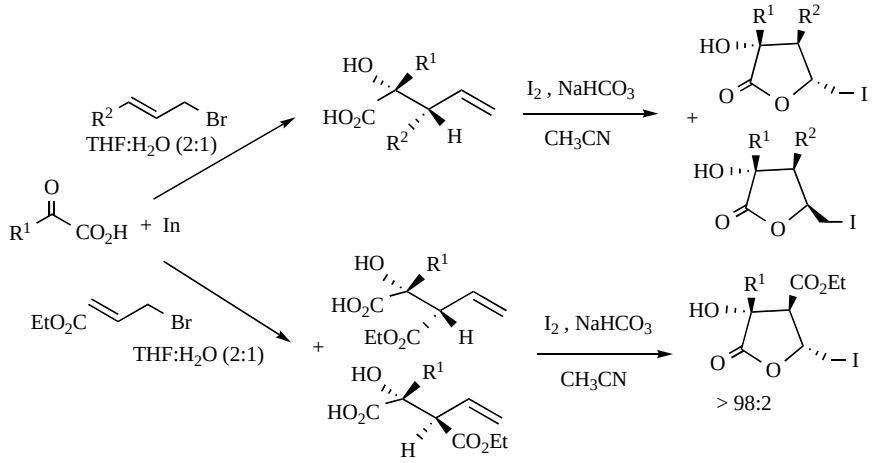
Scheme 12. Preparation of α,β–epoxy-γ-lactones from an optically pure epoxide.

reactive intermediates with carbonyl compounds gave α,β-epoxy-γ-butyrolactones after deblocking the oxazoline moiety [178,179]. This methodology has been successfully extended to the preparation of optically pure α,β-epoxy-γ-butyrolactones from optically pure epoxides (Scheme **12**).

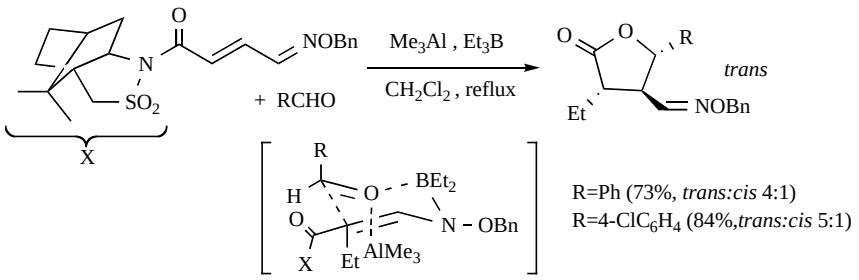
With oxazolinylaziridines, the same authors prepared α,β-azirido-γ-lactones with a similar methodology. In this case, the chemical and configurational stability of the lithiated species depend on the N-substituent in the aziridine ring [180].

Within the context of aldol type reactions, we should mention Maycock *et al.* who described the stereospecific reaction of lithium enolates derived from the thioester of tartaric acid acetal with a selection of aliphatic and aromatic aldehydes. Good chemical yields and high stereoselectivity were achieved [181].

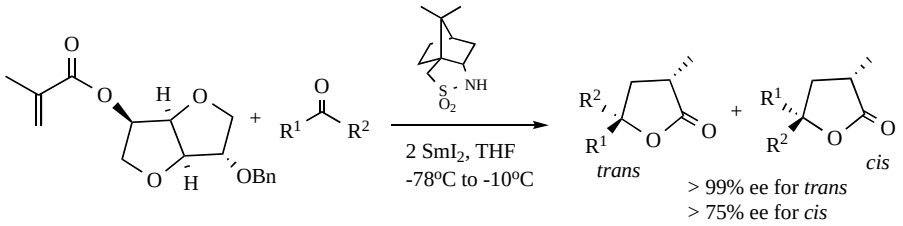
Kumar *et al.* [182] described the glyoxalic, phenylglyoxalic and piruvic acids Indium-mediated allylation with allyl and cinnamyl bromides and ethyl 4-bromocrotonate to provide the respective 2-allyl derivatives of such 2-oxocarboxylic acids. The reactions follow Cram's chelation model with Indium and give *syn* addition products as the major or sole products. As regards the reactions with cinnamyl bromide and ethyl bromocrotonate, allylation proceeds with high γ-regio and diastereoselectivities. These Z-allyl derivatives undergo diastereoselective iodocyclizations and provide 3-hydroxy-γ-lactones with OH and CH_2I moieties placed *syn* to each other as the major product (Scheme **13**).



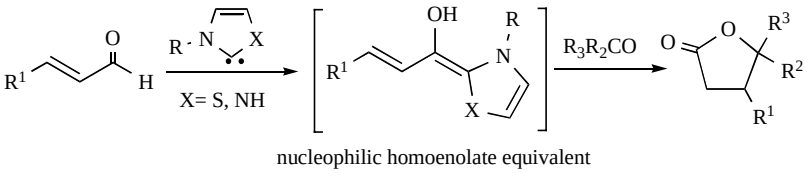
Scheme 13. Approach to g-lactones from allylation of 2-oxoacids catalized by In.



Scheme 14. Tandem radical-addition-aldol type reaction of an α,β–unsaturated oxime ether with aldehydes.



Scheme 15. Reaction of α,β–unsaturated esters with ketones in a SmI2-mediated reductive coupling.



Scheme 16. N-Heterocyclic carbene-catalyzed generation of homoenolates: direct way to γ-lactones.

When this reaction is applied to 2-oxoglutaric acid [183,184], it leads to 2-(1-phenylallyl)- and 2-[(1-ethoxycarbonyl)allyl]- γ-lactone derivatives, which undergo an intramolecular iodocyclization to provide bilactones with a 72%-83% yield.

Naito *et al.* extended the usefulness of Oppolzer's camphorsultam as a quiral inducer by developing a tandem radical-addition-aldol-type reaction of an α,β-unsaturated oxime ether with aldehydes mediated by Me_3Al and Et_3B [185] (Scheme **14**).

Another radical addition followed by aldol condensation is that described by Bertrand *et al.* [186,187]. In this case, the authors described a ZnR_2-mediated radical addition to chiral N-enoyloxazolidinones (α,β-unsaturated diamides) in the presence of benzaldehyde. Diastereoselectivity was sensitive to the nature of both the substrate and radical. Continuing with radical alkylations, a different aldol-type methodology to build the carbon skeleton through C4-C5 bond formation is the use of a Michael-type reaction. Fagnoni *et al*. developed a convenient route to γ-lactols and γ-lactones through a radical alkylation of α,β-unsaturated aldehydes in organic and organic-aqueous media [188]. By using alcohols as radical precursors, the radical formed by hydrogen abstraction with an excited sensitizer attacks the electrophilic olefin at the β-position and finally yields the correspondent γ-hydroxy aldehyde that leads to the desired γ-lactol which, without isolation, may be oxidized to γ-lactones by Br_2, $BaCO_3$.

Alternatively, Steckhan *et al.* [189] showed that when α-hydroxyalkylsilanes were used as radical precursors, α-cyano-γ-lactones were obtained with the addition of α-hydroxyalkyl radicals to methyl acrylates. α-Hydroxyalkylsilanes allowed a one-step generation of substituted γ-lactones via a PET catalyzed generation of α-hydroxyl radicals and their addition to electron-poor methyl acrylates.

Another new methodology worthy of mention is reductive coupling induced by SmI_2. Lin *et al.* developed a SmI_2-induced reductive coupling of chiral 2-alkyl acrylates derived from Isosorbide with several ketones. This reaction takes place through the protonation of Samarium enolate. Therefore, a combination of a chiral 2-alkylacrylate and a hindered proton source is crucial for the success of the asymmetric synthesis [190,191]. The use of (-)-2,10-camphorsultam as a proton source has given the best *e.e.* values [192], and there is also the possibility of using a carbohydrate-derived amide as both a chiral auxiliary and a proton source which has also obtained good results [193,194] (Scheme **15**).

Using N,N-dibenzyl-protected (*S*)-α-amine aldehydes and (*1S,2R*)-N-methyl-ephedrinylacrylate, Fukuzawa *et al.* synthetized γ-aminoalkyl-substituted γ-butyrolactones with the same methodology and obtained good yields and high diastereoselectivities [195].

Procter *et al.* applied this methodology to couple ketones and β-alkoxyacrylates in the synthesis of an antifungal γ-butyrolactone [196]. By using an ephedrine chiral linker, the authors developed a solid-phase alternative [197,198]. Padrón *et al.* applied this methodology to the synthesis of *cis*-β-alkoxy-γ-alkyl-γ-lactones [199] as novel antitumour compounds.

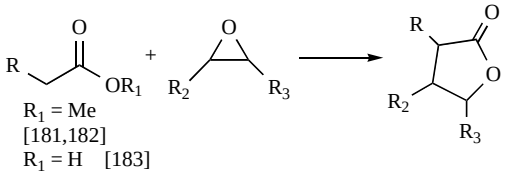
A different approach to γ-lactones used by several authors is the N-heterocyclic carbene-catalized generation of homoenolates. They act as a nucleophilic reactive with another aldehyde or ketone to give adducts able to direct intramolecular cross-linking. Bode [200] and Burstein *et al.* [201,202] described this process specifically for α,β-unsaturated aldehydes or ketones, while Nair *et al.* obtained either spiro γ-butyrolactones in the reaction of enols and 1,2-dicarbonyl compounds [203], or 4,5,5-trisubstituted γ-lactones when diaryl-1,2-diones were used as an electrophile [204]. Zhai *et al.* described the same reaction from benzoins [205] (Scheme **16**).

Two other procedures may be mentioned in this subchapter: the stereoselective synthesis of pentacarbonyl(3-oxa-2-bicyclo[3.1.0] hexylidene)tungsten compounds on the route to cyclopropane-γ-lactones [206] and the setereoselective synthesis of *trans*-β-substituted-γ-ferrocenyl-γ-lactones via ammonium ylides [207]. Moderate to good yields were obtained, and a mechanistic study was described.

4.3. γ-Lactones by C-O Cyclization after C3-C4 Bond Formation

Taylor *et al*. obtained highly substituted γ–lactones from ester enolates and 1,2-dioxines as masked *cis*-γ–hydroxy enones. This reaction afforded good yields and a high diastereoselectivity was obtained as a result of an *anti* 1,4-addition [208].

The ring opening of epoxides with enolates, in the presence of a Lewis acid, is a useful reaction to generate γ–lactones (Scheme **17**). Saičić *et al*. used $TiCl_4$ to promote the reaction of silyl ketene acetals with epoxides, followed by an acidic work-up, which afforded butanolides with moderate yields. The reaction was regioselective with epihalohydrins, and occurred at the less substituted end of the epoxide [209,210]. By using the dianion of carboxylic acids methodology with previously activated epoxides with LiCl as a Lewis acid, Parra *et al.* obtained good yields, but low diastereoselectivitities, in the synthesis of the corresponding γ–lactones [211,212].



Scheme 17. Ring opening of epoxides with esters or acids.

These reactions may also be done by using others enolates as nucleophiles. Jacobsen and Movassaghi described a new route to γ–butanolides in a single step. They used 1-morpholino-2-trimethylsilyl acetylene and terminal epoxides as starting materials with $BF_3{\cdot}OEt_2$ as the Lewis acid [213]. The cyclic keteneaminals intermediate in the ring-opening of epoxides with 1-morpholino-2-trimethylsilyl acetylene provides an opportunity for the direct synthesis of more highly functionalized γ–butanolides by simply changing the work-up. This reaction provides good yields and affords high enantiomeric excess.

Manganese(III) acetate was found to be a good initiator for the radical addition of enolizable compounds to alkenes. Brun *et al*. carried out the addition of malonic acid to cinnamic esters, a one-step reaction that provides functionalized *trans*-4,5-disubstituted–γ–butyrolactones with low and moderate yields [214].

Biermann and Metzger used α–halocarboxylic acids esters instead of malonic acid. In this case, the reaction was initiated by an electron transfer from copper and the authors described similar results. Furthermore, the reaction was applied to intramolecular cyclations using $SnCl_2$/AgOAc as an initiator to obtain better results [215].

By applying a similar process to the Kharasch reaction, Shvo and Somech designed a synthetic route to γ–substituted γ–butyrolactones from alkenes and α,α-dichloroesters in the presence of CuCl in catalytic amounts and Fe(0) in stoichiometric amounts [216]. The conversion of this reaction was high, although *bis*-lactones may form as secondary products.

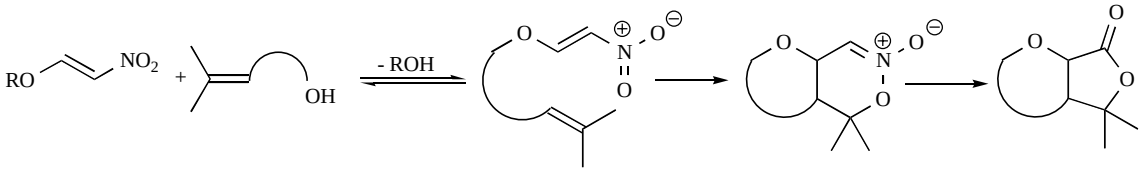
Quayle *et al.* proved that atom transfer cyclization reactions (ATRC) may be used in the rapid and stereoselective synthesis of functionalized γ–lactones [217]. By using 3-phenylprop-2-enyl trichloroacetate derivates and CuCl/dHbipy in catalytic amounts, they obtained 3,3-dichloro–γ–lactones with good yields, but with poor diastereoisomeric excess.

Diels-Alder reactions may be also used for the synthesis of γ–lactones. Wada *et al*. developed a tandem reaction of (*E*)-1-ethoxy-2-nitroethylene with δ,ε-unsaturated alcohols using a catalytic amount of Lewis acid, such as $Yb(OTf)_3$ and $Ni(ClO_4)_2{\cdot}6H_2O$. The products of this reaction were *trans*-fused bicyclic γ–lactones. This process involved the stereoselective tandem transetherification-intramolecular hetero Diels-Alder reaction, leading to bicyclic nitronates and the sequential transformation of the nitronate moiety to lactone with good yields [218] (Scheme **18**).

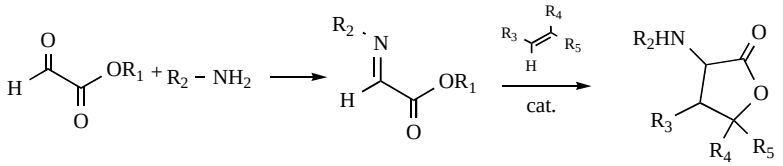
Finally, two research groups worked on obtaining α–amino γ–lactones. Li *et al*. reported the formation of these lactones by an $InCl_3$-mediated or $Sc(OTf)_3$-catalyzed three-component reaction: alkenes, glyoxylates and amines, where the substitution of the starting material highly influenced the yields [219]. Alternatively, Wang *et al.* found that Ytterbium(III) triflate can catalyze the electrophilic cyclization of some glyoxalate-derived unsaturated imines. These cyclization reactions gave exclusively fused amino γ–lactone products with good stereoselectivity and moderate yields [220] (Scheme **19**).

4.4. γ-Lactones by C-O Cyclization after C2-C3 Bond Formation

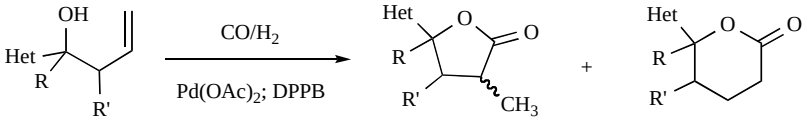
Finally, we will consider C2-C3 bond formation before C-O cyclization. For this purpose, two different routes may be found in the literature: carbonylations and electrocyclic reactions.



Scheme 18. Synthesis of trans-fused bicyclic lactones.



Scheme 19. Synthesis of amino actones from glyoxylates.



Scheme 20. Cyclocarbonylation of α–(hydroxyl)homoallylic alcohols by Pd(II)/DPPB/CO/H2.

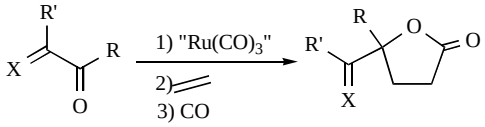
Troisi *et al*. described how α-(Heteroaryl)homoallylic alcohols underwent cyclocarbonylation reactions under the pressure of CO and H_2, catalyzed by Pd(II) and complexed with phosphine ligands to give five- and six-membered lactones with moderate to good yields. Changes in pressure (generally 300 psi of CO and 300 psi of H_2), reaction time or temperature do not affect the regiochemistry of these reactions. In contrast, δ–lactones can be obtained regioselectively by using toluene as a solvent and 1,4-bis(diphenylphosphino)butane (DPPB) as a ligand, whereas five-membered ring products are obtained with CH_2Cl_2 as a solvent and BINAP as a ligand. γ–lactones are formed with low diastereoselectivity (*trans*>*cis*) [221] (Scheme **20**).

Kitching *et al*. applied a similar methodology to ene-diols to obtain tetrahydrofuran-bicyclic-γ-lactones, and described a hydrolitic kinetic resolution of epoxides [222].

Schmidt *et al*. combined a Ru-catalyzed ring-closing metathesis with a Rhodium-catalyzed hydroformylation of homoallylic alcohols to lead to tetrahydropyran spirocyclic γ–butyrolactones [223].

A route to the γ-lactone ring with atom economy is that involving a formal [2+2+1] cycloaddition of an alkene, a carbonyl compound and CO. Crowe *et al*. described how this hetero-Pauson-Khand reaction can convert δ,ε–unsaturated ketones and aldehydes into bicyclic γ–butyrolactone products [224]. They reported a general catalytic cyclocarbonilation of enals and enones using a chiral ansa-titanocene catalyst. Diastereofacial selectivity was investigated.

Nevertheless, Murai *et al*. were the first to describe a catalytic synthesis of heterocycles via an intermolecular cabonylative [2+2+1] cycloaddition [225]. They demonstrated that $Ru_3(CO)_{12}$ catalyzes the intermolecular cyclocoupling of ketones (or aldehydes), alkenes (or alkynes) and CO. They analyzed the differences caused by additive or substituent effects, along with the dependence of the reaction on parameters such as the pressure of ethylene and CO. This enabled them to propose two possible mechanisms (Scheme **21**).



Scheme 21. [2+2+1] Ru3(CO)12-catalyzed intermolecular cyclocouplings.

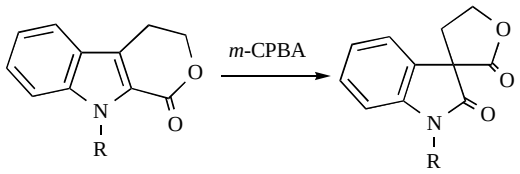
Woerpel *et al.* developed a stereoselective synthesis of γ–lactones by a [3+2] annulation of allylic silanes with chlorosulfonyl isocyanate (CSI), and applied it to accomplish an enantioselective total synthesis of (+)-Blastmycinone [226]. Their studies of reactivity of α-silylmethyl-substituted allylic silanes in the [3+2] annulation reaction enabled them to find that a reaction with $ClSO_2NCO$ gave a N-Chlorosulfonyliminolactone as the major product. The hydrolysis of the intermediates afforded γ-lactones (Scheme **22**). They also synthesized a series of allylic silanes to investigate competition between the annulation across the C=N and the C=O bond to develop the reaction into a route to γ-lactones.

Finally, Rudler *et al*. described how the carbene carbon of 1,4-alkene and alkyne carbene complexes of chromium and tungsten reacts with nucleophiles such as hydrides to give polycyclic lactones upon CO and alkyne (or alkene) insertions [227].

5. MISCELLANEOUS

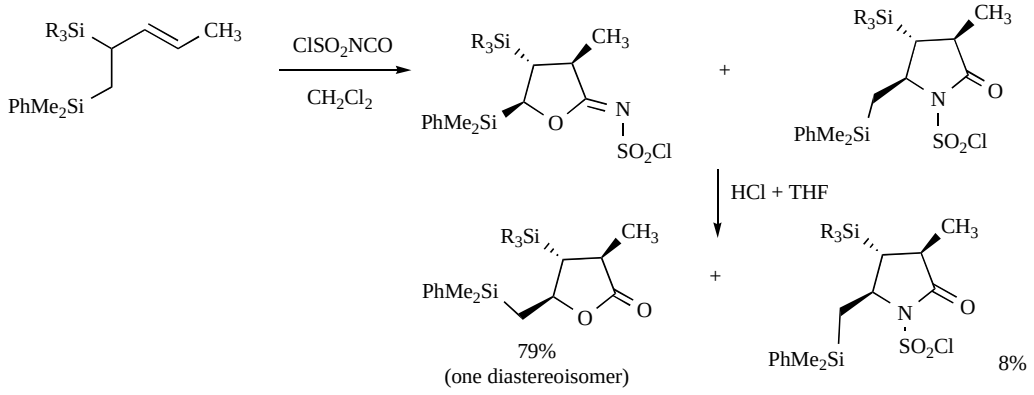
The Baeyer-Villiger reaction is a useful methodology for the synthesis of γ-butyrolactones. Using cyclobutanones and applying different oxidative processes, butanolides can be obtained whilst preserving the stereochemistry of the starting material. The use of different oxidants and reaction conditions are continuously optimized [228-236] and applied to the synthesis of natural products such as (±)-Asarinin, (±)-Epimagnolin A or (±)-Fargesin [237].

Spiroindolin-2-one γ–lactones may be obtained via the oxidative cleavage of indole δ–lactones with *m*-chloroperbenzoic acid. The reaction was carried out with moderate yields [238] (Scheme **23**).

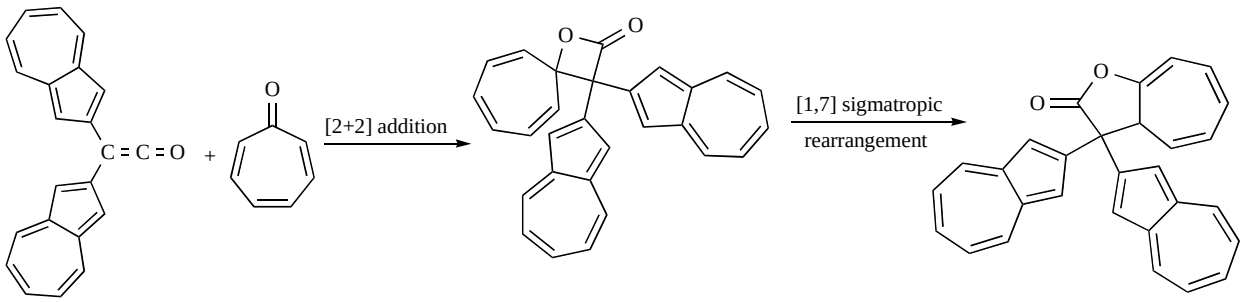


Scheme 23. Synthesis of spiroindolin-2-one -lactones.

γ–Lactones can also be obtained via β–lactones rearrangements. *cis*-Fused bicyclic γ–lactones were prepared by Black in a three-step sequence featuring the stereospecific rearrangement of spiro bicyclic β–lactones [239].



Scheme 22. [3+2] Annulation of allylic silanes with chlorosulfonyl isocyanate.



Scheme 24. Reaction of di(2-azulenyl)ketene with tropone.

Fujimori *et al.* used di(2-azulenyl)ketene, generated by the thermal decomposition of diazodi(2-azulenyl)ethanone, and tropone in the formation of γ-lactones with good yields [240]. This formation can be explained by considering a two-step reaction mechanism: a [2+2] addition and the subsequent [1,7] sigmatropic rearrangement (Scheme **24**).

Ethenetricarboxylate derivatives have been used as highly electrophilic C2 components in Lewis acid-promoted [2 + 2] and [2 + 1] cycloadditions. With this approach, Yamazaki *et al.* described the synthesis of highly functionalized γ-lactones with heterogeneous results [241].

As a final approach, Cheng and Rayabarapu carried out the reaction of dimethyl-7-oxabicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate with alkyl propiolates to afford the corresponding reductive coupling/cyclization products and bicycle[3.2.1]γ-lactones which resulted in good yields with a remarkably high regio- and stereoselectivity [242].

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