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Microwave Radiation Applied to the Synthesis of γ-butyrolactone Derivatives

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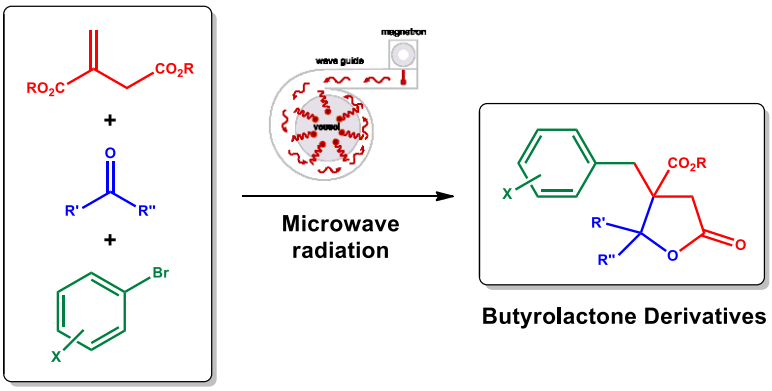
Many natural products with a broad spectrum of biological effects bear the γ-butyrolactone ring. Given the difficulty in isolating large amounts of butyrolactones from natural sources, interest in synthesizing structural analogs of these compounds and in studying their biological properties has increased. In this review, we summarize the main synthetic methodologies to construct γ-butyrolactone derivatives by using multicomponent processes.

Graphical abstract



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1. Introduction

Natural products exhibit a broad spectrum of biological effects and are important leads in drug discovery. In traditional medicine, these products and their various synthetic analogs have often been used to treat several diseases [1]. γ-Lactones are widely distributed in nature. About 10% of all the natural products present a γ-butyrolactone skeleton that occurs as mono-, di-, or tri-substituted monocyclic lactones, but this skeleton may also be part of more complex frameworks (Figure 1) [2].

γ-Butyrolactones are a structural feature of various natural products, such as sesquiterpene lactones [3], and lignan lactones [4], and are produced by algae, sponges, fungi, and liverworts [5,2g]; some γ-butyrolactones have been also isolated from *Streptomyces* [6]. The γ-lactone subunit has been associated with numerous anti-parasitic activities, including leishmanicidal [7], nematocidal [8], and antiplasmodial actions [9], as well as other biological activities [10], like antitumor [11], antibacterial [12], antiviral [13], and antiprotozoal [14] action, among other effects [15]. Tribenzylbutyrolactones, known as maculalactones, are among these compounds. They have been isolated from the cyanobacterial species *Kyrtuthrix maculans* [16]. Maculalactone A (Figure 1) is the most abundant secondary metabolite in *K. maculans* and may provide this marine cyanobacterium with chemical defense against many marine organisms [17], but the yield of this compound extracted from the cyanobacterium is very low, *ca.* 1 mg/g [17a].

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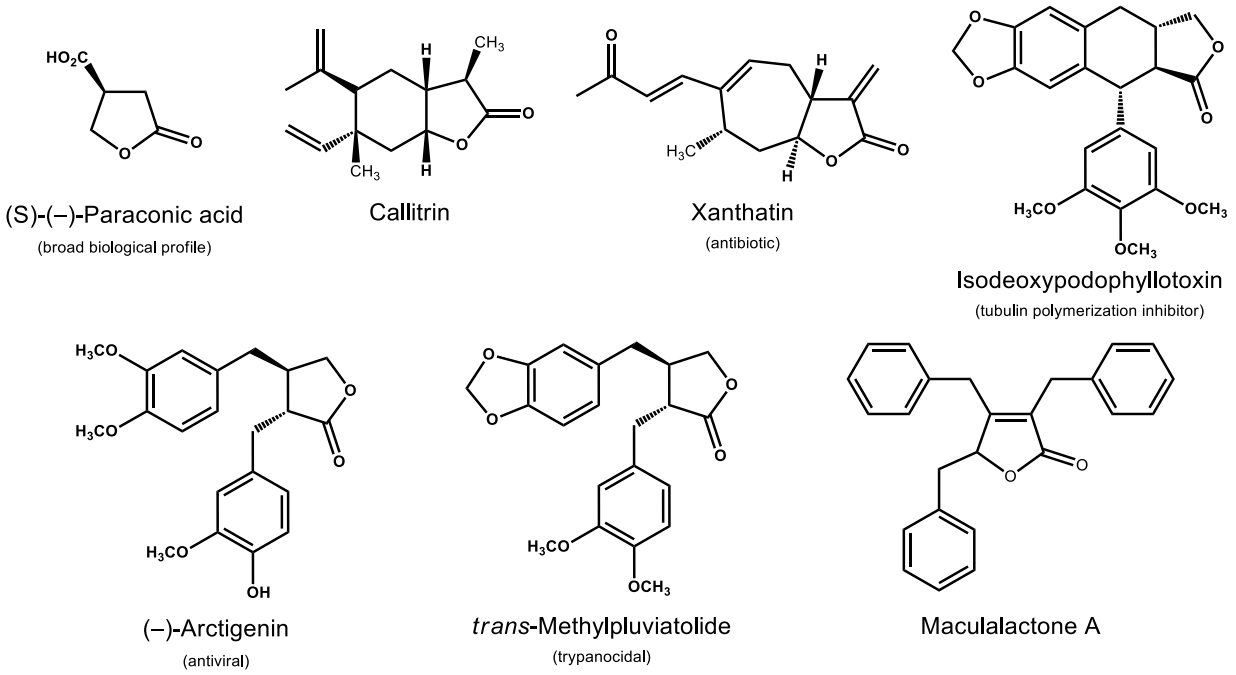


Fig. 1. Examples of γ-butyrolactones and some biological activities.

The diverse biological properties of butyrolactones, the difficulty in isolating large amounts of them from natural sources (because of their low concentration therein), and the high costs and difficulties inherent in their isolation have aroused great interest in synthesizing structural analogs of these compounds and in extending studies on their biological properties. Several γ-butyrolactone-containing drugs have been FDA-approved and used in the clinical setting for diverse purposes. For example, these drugs have been employed as diuretics, anticancer agents, contraceptive drugs, and anti-glaucoma agents and in the treatment of heart diseases [18].

To enhance the biological activities of biologically active natural products, research into their synthesis and structural modification has grown over the last decade, and several focused reviews have been published [2-19]. Recently published studies have shown the development of new multicomponent reactions (MCRs), which are efficient for simultaneous formation of several carbon-carbon bonds and carbon-heteroatom bonds in a single reaction step [20]. However, the synthesis of γ-butyrolactones by multicomponent processes has been little reported [21]. The most common examples described in the literature involve preparation of arylnaphthalenolactone derivatives [22], or fused lactones [23].

In this review, we summarize the main synthetic methodologies to construct γ-butyrolactones by using multicomponent processes. We describe mainly the methodologies that employ microwave radiation to accelerate these synthetic processes.

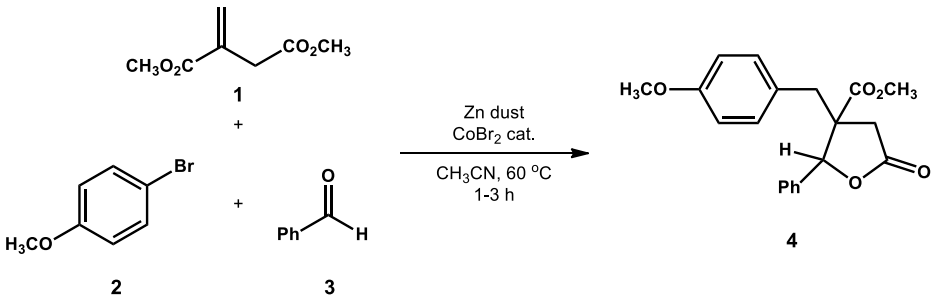
2. Synthesis of γ-Butyrolactone Derivatives by Multicomponent Reactions

The interest in developing new methodologies to synthesize compounds bearing γ-butyrolactones in their structures has increased, and MCRs have been targeted [24]. MCRs have aroused significant interest in organic synthesis because they can be used to achieve complex products from readily available starting materials in an environmentally-friendly manner. MCRs are advantageous because they (i) incorporate most or all the atoms of the reagents into the final product in few steps; (ii) usually involve a one-pot reaction; and (iii) allow facile product purification [25].

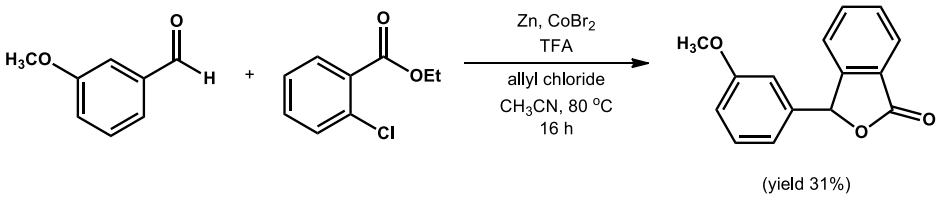
In 2009 and 2010, Le Floch, Le Gall, and co-workers [26] developed an interesting MCR from dimethyl itaconate (**1**) to synthesize paraconic ester analogs (**4**); more specifically, 2,3-disubstituted and 2,2,3-trisubstituted-3-methoxycarbonyl-γ-butyrolactones, as shown in Scheme 1. This MCR consists of a cobalt-catalyzed domino process that formally involves *in situ* metalation of an aromatic bromide, conjugate addition to dimethyl itaconate, aldolization with a carbonyl compound, and final cyclization into a five-membered lactone. In this process, cobalt(II) bromide and zinc dust are used as catalyst and reducer, respectively. The authors also reported how several parameters, including temperature, amounts of dimethyl itaconate and cobalt bromide, zinc dust activation method, and work-up conditions, influence the reaction efficiency and proposed a detailed mechanism of reaction.

Later, this same research group used this MCR to obtain various paraconic ester analogs with an important range of functions compatible with the process. The authors evaluated the biological activities of the obtained compounds against a representative set of cancer cell lines (KB, HCT116, MCF7, and HL60) [27]. While most molecules exhibited low to moderate background activity, one of the molecules (compound **4c** shown in Table 1) displayed promising antitumor activity, with cellular growth inhibitions higher than 50% in the four tested lines, and with IC_{50} values in the range of 10^{-7}–10^{-6} mol/L [11a, 27].

In 2019, Presset, Le Gall, and co-workers [28] extended this type of reaction and used it to prepare phthalides, as shown in Scheme 2. In this case, the authors attributed the moderate yield (31%) and the limited reactivity to the presence of the electron-withdrawing group at the *ortho* position, which strongly decreases the nucleophilicity of the transient organometallic species.

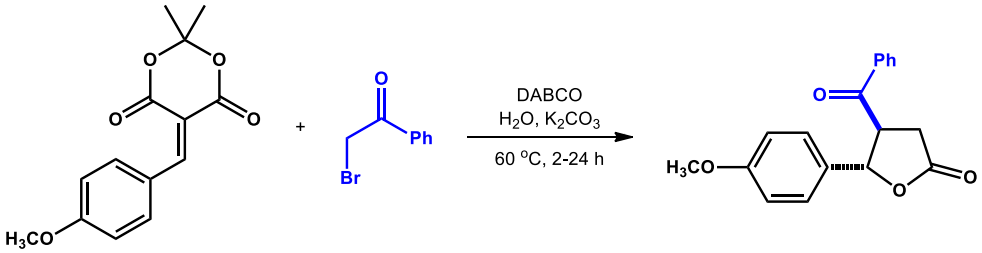


Scheme 1. Multicomponent reaction developed by Le Floch, Le Gall, and co-workers [26].



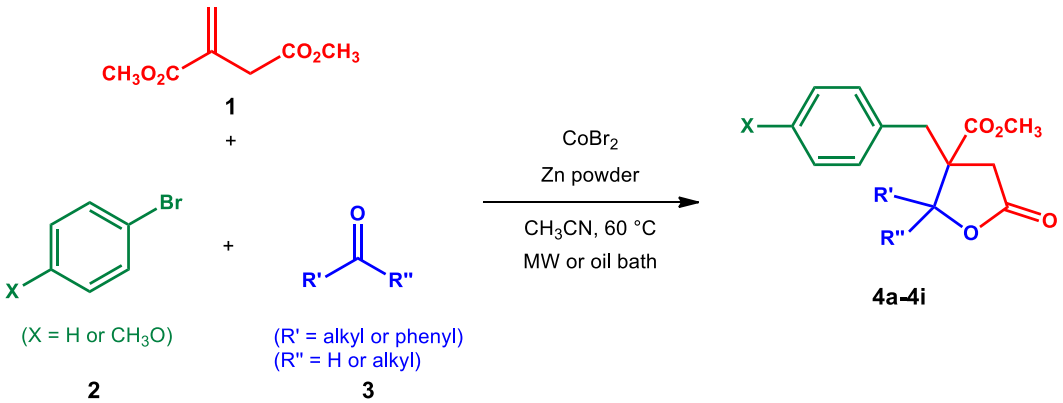
Scheme 2. Co-catalyzed Barbier/lactonization domino reaction [28].

More recently, in 2020, Drennhaus and co-workers [21b] developed a one-pot method to obtain *trans*-β,γ-disubstituted γ-butyrolactones from benzylidene Meldrum's acid derivatives and α-bromo carbonyl compounds, as shown in Scheme 3. The γ-butyrolactones were obtained in yields between 32–99% with excellent diastereoselectivities (>95:5) via a DABCO-mediated [2+1] annulation.



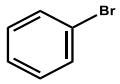
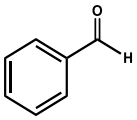
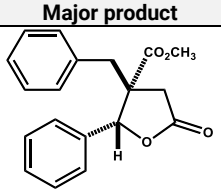
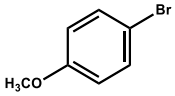
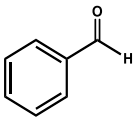
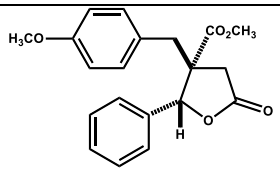
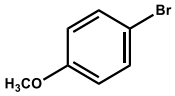
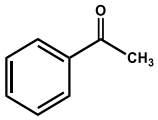
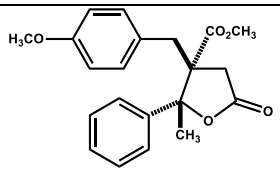
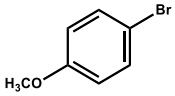
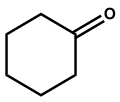
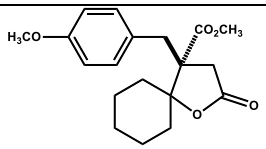
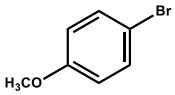
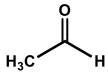
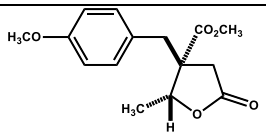
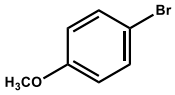
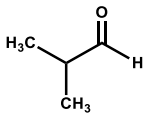
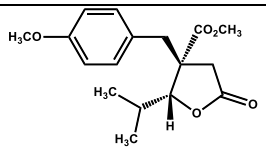
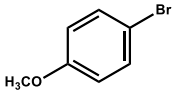
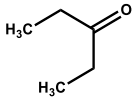
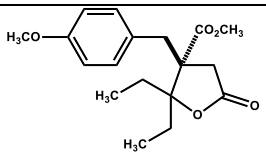
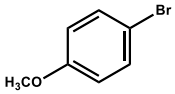
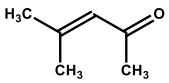
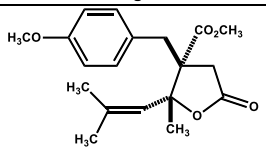
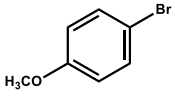
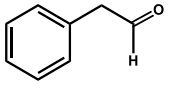
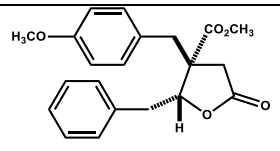
Scheme 3. *Trans*-β,γ-disubstituted γ-butyrolactone formation [21b].

Over the last decade, microwave radiation has gained popularity as a powerful tool to synthesize various compounds fast and efficiently. This process is advantageous over conventional thermal heating because it reduces reaction time, improves yields, and suppresses the generation of side products [29]. Aiming to synthesize several biologically active γ-butyrolactones, Donate and co-workers [30] used microwave radiation as heat source to promote fast and efficient synthesis of a series of γ-butyrolactone derivatives through cobalt-catalyzed MCRs [26]. This modified methodology improved the yield of reactions with specific types of substrates after only a few minutes [30]. Indeed, this MCR gave the target compounds **4a-i** (Scheme 4) in good yields when the authors applied microwave radiation as heat source. Table 1 summarizes the results of these reactions and compares the yields obtained by using microwave radiation or conventional heating with an oil bath at the same temperature.



Scheme 4. Preparation of compounds **4a-i** by multicomponent reaction.

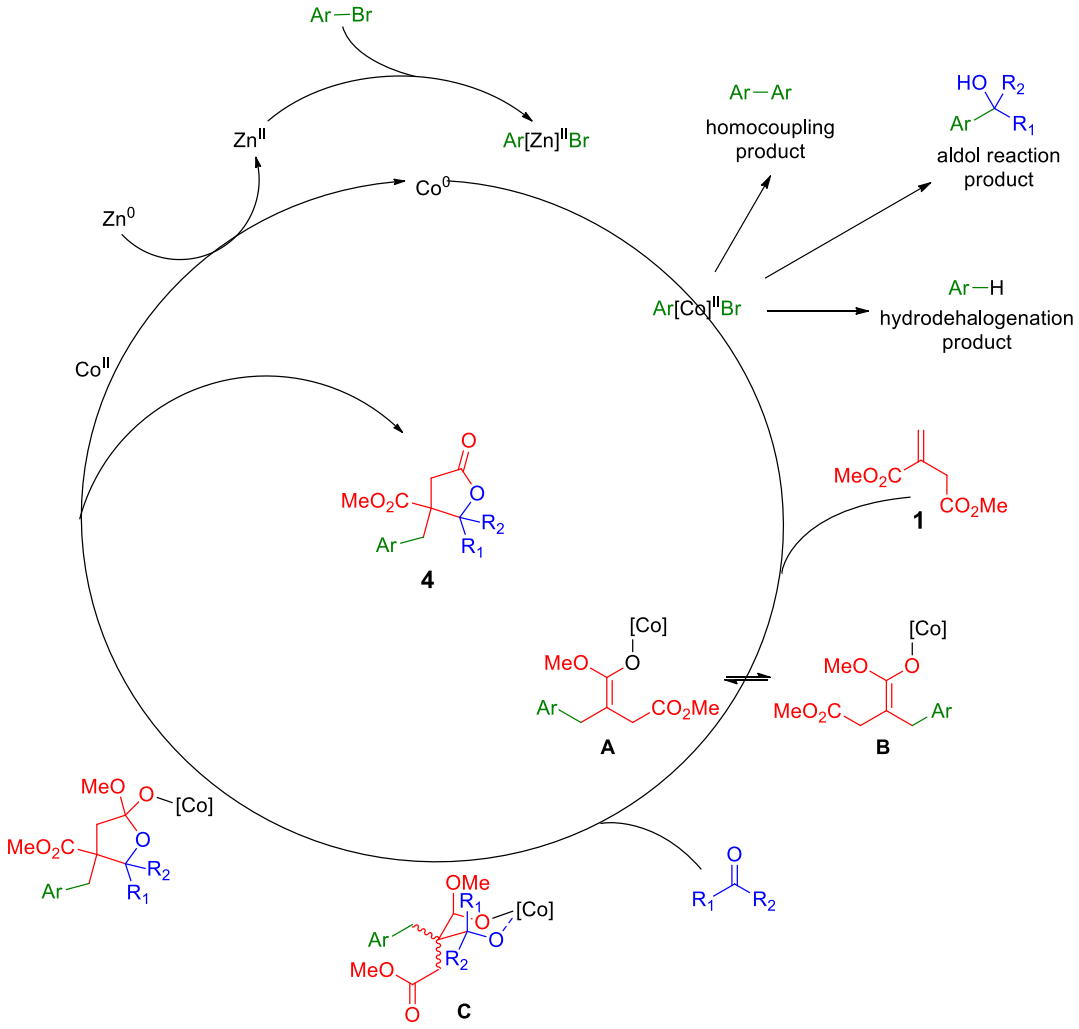
Table 1. γ-Butyrolactone derivatives **4a-i** produced *via* the multicomponent reaction depicted in Scheme 4.[a]

Entry	Halide (2)	Aldehyde/ketone (3)	Major product	Yield [b]
1			 **4a**	85% (MW) 35% (oil bath)
2			 **4b**	96% (MW) 70% (oil bath)
3			 **4c**	82% (MW) 13% (oil bath)
4			 **4d**	80% (MW) 20% (oil bath)
5			 **4e**	81% (MW) 18% (oil bath)
6			 **4f**	88% (MW) 24% (oil bath)
7			 **4g**	86% (MW) 13% (oil bath)
8			 **4h**	85% (MW) 30% (oil bath)
9			 **4i**	90% (MW) 83% (oil bath)

[a] The reactions were conducted under argon atmosphere with acetonitrile (5 mL), dimethyl itaconate **1** (2 g, 13 mmol), an aldehyde or a ketone (2.5 mmol), an aryl bromide (4 mmol), and zinc powder (12 mmol). After brief stirring at room temperature, cobalt bromide (0.6 mmol), trifluoroacetic acid (0.03 mL), and 1,2-dibromoethane (0.05 mL) were successively added. The reaction mixture was heated at 60 °C for 1–3 h in an oil bath, or irradiated for 10–20 min in a CEM Discovery® focused microwave oven at 60 °C and 150 W. [b] Isolated yield.

The recent increase in the number of publications on cobalt-catalyzed MCRs reveals the importance of cobalt catalysis. Anilkumar and co-workers [31] recently published a review explicitly examining MCRs catalyzed by cobalt. Le Floch and co-workers were the first to propose a reaction mechanism for cobalt-catalyzed MCRs [26]. Scheme 5 shows

this mechanism: it starts with metallic zinc reducing cobalt(II), followed by formation of an organometallic compound originating from aromatic bromide, which then reacts with dimethyl itaconate (**1**) by conjugate addition, producing enolates **A** and **B**. These enolates could react with a carbonyl compound through a Zimmerman-Traxler transition state, to generate intermediate **C**, which produces the γ-butyrolactone **4** by a lactonization process. The by-products observed by the authors originate from homocoupling of the organometallic reagent, and the aldol product results from reaction between the organometallic reagent and the carbonyl compound.



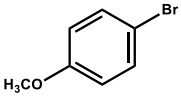
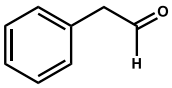
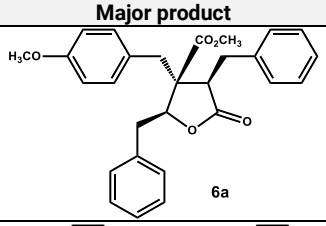
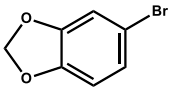
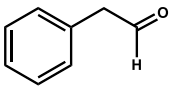
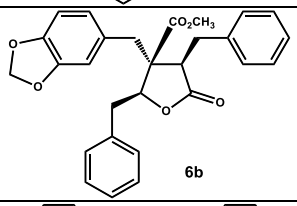
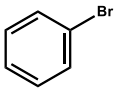
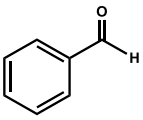
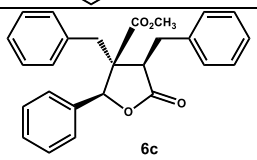
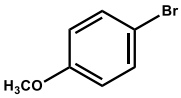
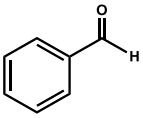
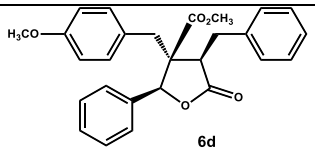
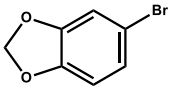
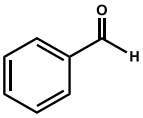
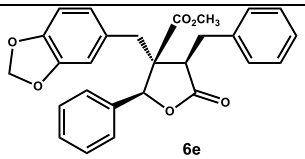
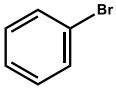
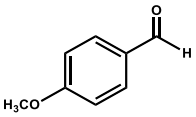
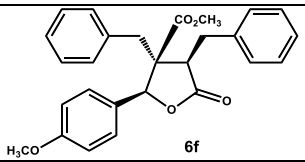
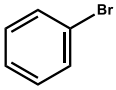
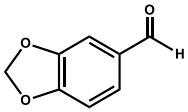
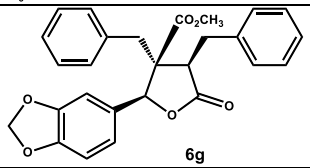
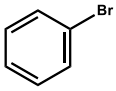
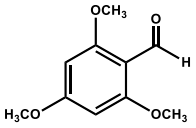
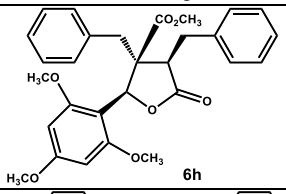
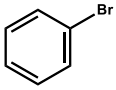
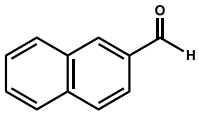
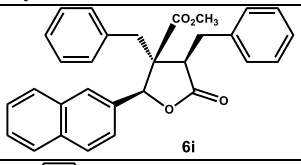
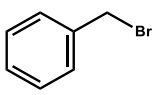
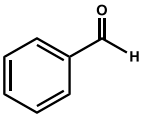
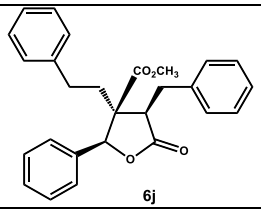
Scheme 5. Proposed mechanism for the multicomponent reaction shown in Scheme 4 [26].

Recently, Crotti and collaborators investigated this MCR and demonstrated that the mechanism of this cobalt-mediated one-pot reaction can be investigated by using pressurized sample infusion electrospray ionization mass spectrometry (PSI-ESI-MS) and FTIR spectroscopy [32]. The use of charge-tagged aryl halides allowed cobalt(II)-promoted hydrodehalogenation products to be detected. Although these products were also detected by the off-line ESI-MS monitoring, the ability of PSI-ESI-MS to track real-time changes in the reaction mixture composition proved that cobalt(II) was responsible for the undesired transformation. The occurrence of cobalt(II)-promoted hydrodehalogenation as a side reaction in this MCR had not been considered in previous mechanistic proposals and represents an important mechanistic consideration. More recently, Rodrigues, Eberlin and Neto [20b] reviewed a number of techniques that are used to elucidate the mechanisms of MCRs. The major strategy has been to use ESI-MS(/MS) monitoring and charge tagging, and several examples of intricate MCR mechanisms have been illustrated. This review article compared several techniques that shed light over the favored pathway selected from the myriad of alternatives theoretically available for MCRs, in view of the greater number of possible intermediates in MCRs when compared to traditional reactions, making this task of mechanistic investigation harder and more complicated.

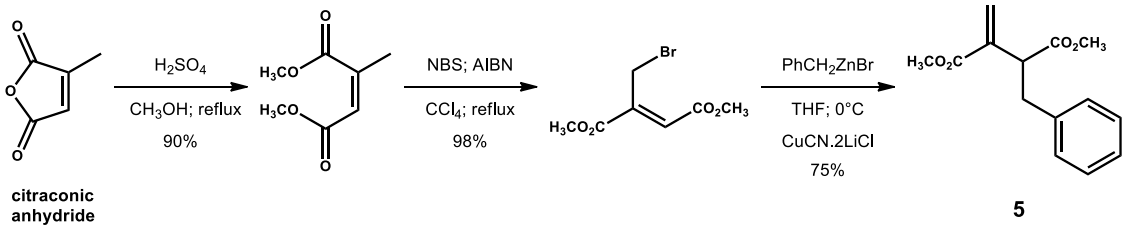
By using the same cobalt-catalyzed MCRs, Donate and co-workers [33] also employed microwave radiation to obtain maculalactone derivatives. First, the authors used an easy three-step synthesis described by Kar and Argade [34] to transform the commercial citraconic anhydride into dimethyl 2-benzyl-3-methylenesuccinate (**5**), as shown in Scheme 6. For convenience, in the third stage of this preparation, the authors replaced the alkylmagnesium reagent employed in the original publication with a benzylic zinc reagent, obtained *in situ* by direct zinc insertion in the presence of LiCl according to the methodology described by Knochel and co-workers [35].

With compound **5** in hand, the authors prepared the maculalactone derivatives **6a-j** by the MCR shown in Scheme 7 by the microwave radiation technique. Table 2 summarizes the results obtained in the MCRs of compound **5** with the various types of halides and aldehydes.

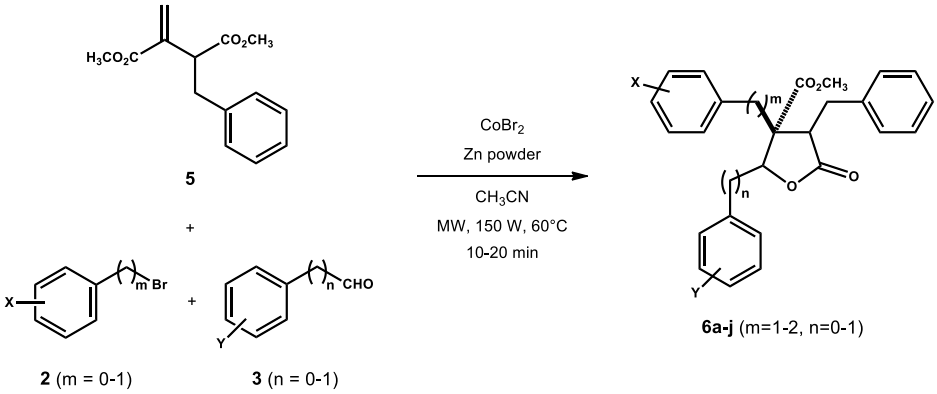
Table 2. Maculalactone derivatives **6a-j** produced *via* the multicomponent reaction depicted in Scheme 7.[a]

Entry	Halide (2)	Aldehyde (3)	Major product	Yield (d ratio)[b]
1			 **6a**	31% (62:16:14:8)
2			 **6b**	42% (62:18:12:8)
3			 **6c**	89% (73:14:8:5)
4			 **6d**	83% (78:19:3:0)
5			 **6e**	70% (80:11:7:2)
6			 **6f**	93% (64:16:12:8)
7			 **6g**	66% (57:17:15:11)
8			 **6h**	82% (55:35:8:2)
9			 **6i**	35% (57:20:15:8)
10			 **6j**	52% (53:30:17:0)

[a] The reactions were conducted under argon atmosphere, by using acetonitrile (5 mL), compound **5** (13 mmol), an aldehyde (2.5 mmol), an aryl bromide (4 mmol), and zinc powder (12 mmol). After brief stirring at room temperature, cobalt bromide (0.6 mmol), trifluoroacetic acid (0.03 mL), and 1,2-dibromoethane (0.05 mL) were successively added. The reaction mixture was irradiated for 10-20 min in a CEM Discovery® focused microwave oven at 60 °C and 150 W. The major diastereoisomers were isolated by diastereoselective recrystallization by using a mixture of acetonitrile, methanol, and water (40:40:20 v/v). [b] Yield of isolated products. (d ratio) = Ratio of products in the diastereoisomeric mixture determined by GC-FID.



Scheme 6. Preparation of compound **5** from citraconic anhydride.



Scheme 7. Preparation of compounds **6a-j** *via* a multicomponent reaction under microwave radiation.

Once again, microwave radiation as heat source produced better results than conventional heating with oil bath at the same temperature: the reaction times were shorter, and the product yields were higher in the former case. As shown in Table 2, under conventional heating at 60 °C, the reactions of compound **5** and phenylacetaldehyde with 4-bromoanisole and 1-bromo-3,4-(methylenedioxy)benzene (entries 1 and 2, respectively) produced compounds **6a** and **6b** in very low yields (~5%) after reaction for one hour. Longer heating times led to phenylacetaldehyde decomposition. Application of microwave radiation provided better results because the temperature of the reaction mixture rose fast from room temperature to 60 °C, producing the desired compounds **6a** and **6b** in higher yields (31% and 42%, respectively) after reaction for only 10–20 minutes.

In this MCR, aryl bromides afforded better yields (entries 3–8, Table 2, 66–93%) than alkyl bromides (entry 10). Reaction of benzaldehyde with benzyl bromide in the presence of compound **5** (entry 10) afforded low yield (52%) of compound **6j**, while benzaldehyde and cyclopentyl bromide in the presence of compound **5** did not react under the assessed conditions. Phenylacetaldehyde (entries 1–2) formed the desired products in lower yields (31–42%) than benzaldehyde (entries 3–5, 70–89%). However, depending on the substituents on the aromatic ring of benzaldehyde, the product yield varied widely (entries 4, 6–9, 35–93%). Because obtaining commercially substituted phenylacetaldehyde derivatives is difficult, the effect of their substituents on this reaction has not been tested. Reactions of compound **5** and bromobenzene with several kinds of ketones did not provide the desired products, probably due to the low reactivity of the ketones. Nevertheless, the large variation in yield observed in this MCR may be due to the steric hindrance posed by the benzyl group attached to C2 of compound **5**. Indeed, a similar reaction using unsubstituted dimethyl itaconate (**1**) (which is less sterically hindered) and various aliphatic aldehydes and ketones (see Table 1) did not elicit such behavior and furnished most of the desired products in very good yields [30].

^{1}H and ^{13}C NMR data, two-dimensional NMR techniques (HMQC, HMBC, and ^{1}H-^{1}H COSY), and mass spectrometry aided identification of the structures of all the synthesized compounds **6a-6j** [30,32]. The relative stereochemistry of the compounds was assigned on the basis of NOE difference spectroscopy between the signals of the hydrogens at C2 and C4 of the γ-butyrolactone ring, and the hydrogens at C14 of the benzyl group. NMR analyses revealed that the relative stereochemistry of the major diastereoisomer obtained in all the reactions was always the same, regardless of the reagents. However, the ratio of other diastereoisomers produced in smaller quantities varied greatly, depending on the substituents on the aromatic ring of the halides and aldehydes. This probably resulted from steric congestion of the transition state of the diastereoisomers originating from more substituted reagents [26].

Interestingly, the single-step synthesis of maculalactone derivatives through this MCR afforded γ-butyrolactones with three aromatic substituents and three stereogenic centers (Scheme 7 and Table 2). All the reactions exhibited moderate diastereoselectivity, and their products consisted of mixtures of all four possible diastereoisomers. The relative configuration of the major diastereoisomer was determined by NOEDiff NMR experiments as *anti:anti* from a solid sample obtained from selective crystallization [33]. As the full characterization of the four diastereoisomers was not so clear-cut, the ^{13}C and ^{1}H NMR chemical shifts were calculated and compared to experimental data so that the relative configurations of all the four diastereoisomers could be assigned [36]. The assignment of the relative configurations of the four diastereoisomers of maculalactone derivative **6c** (Table 2), initially deduced on the basis of the mechanism proposed for the MCR (Scheme 5), was confirmed by using the CP3 parameter [37]. This parameter provides high level of confidence as revealed by the calculated CP3 probability. Briefly, DFT/GIAO calculations of ^{1}H and ^{13}C NMR chemical shifts can be used in combination with CP3 to compare experimental and calculated NMR data for complete assignment of all the possible diastereoisomers of a γ-

butyrolactone ring with three stereogenic centers [36]. After that, the absolute configurations of these diastereoisomers were confirmed by X-ray crystallographic analysis [38].

3. Conclusions

In summary, the experimental results described in this review for the synthesis of butyrolactones via MCR clearly indicate that microwave-assisted synthesis significantly increases product yields and reduces reaction time as compared to conventionally heated systems. Furthermore, microwave-assisted synthesis has proven an important strategy to produce several γ-butyrolactone derivatives in a single synthetic step through a cobalt-catalyzed multicomponent reaction.

Acknowledgments

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