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A Cobalt-Catalyzed Multicomponent Approach to Novel 2,3-Di- and 2,2,3-Trisubstituted 3-Methoxycarbonyl-γ-butyrolactones

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A one-pot, three-component synthesis of the title butyrolactones starting from aryl bromides, dimethyl itaconate, and either aldehydes or ketones is described. The cobalt-catalyzed domino process formally involves the in situ metalation of an aromatic bromide, conjugate addition onto dimethyl itaconate, an aldolization reaction with a carbonyl compound and a final cyclization into a five-membered lactone. This procedure is applied to the concise synthesis of a range of functionalized γ-butyrolactones with a methyl paraconate subunit.

Introduction

The γ-butyrolactone subunit is a characteristic feature of many natural products displaying significant biological activities.[1] The substitution pattern of the five-membered ring defines several classes of compounds to which paraconic acids[2] belong. These compounds, bearing a carboxylic acid function at the β position, constitute an important group of γ-butyrolactones that displays antitumor and antibiotic biological activities, and also represents convenient building blocks for the synthesis of compounds of pharmaceutical interest.[3] Although these interesting properties have made them attractive synthetic targets for the organic chemist,[4] the preparation of 2,3-polysubstituted γ-butyrolactones through multicomponent procedures[5,6] has been only scarcely reported.[7]

Recently, we disclosed preliminary results regarding the multicomponent synthesis of some paraconic acid analogues from aryl bromides, aromatic aldehydes and dimethyl itaconate through a domino metalation/conjugate addition/aldol coupling/cyclization process.[8] In this paper, we both confirm the efficient formation of 2,3-disubstituted 3-methoxycarbonyl-γ-butyrolactones and further expand the scope of the procedure by applying the strategy to the preparation of 2,2,3,3-tetrasubstituted γ-butyrolactones through the use of ketones as carbonyl compounds. We also discuss a putative reaction pathway.

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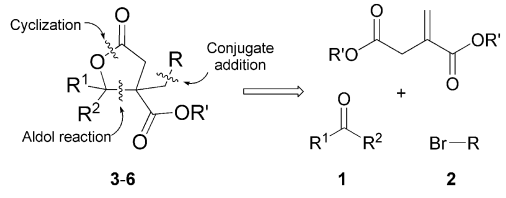
Results and Discussion

As a starting point for the study, we anticipated that a range of 2,3-polysustituted paraconic esters should be accessible through a sequence involving the formation of three single bonds by means of conjugate addition, aldol reaction and cyclization (Scheme 1). We also considered the additional opportunity of turning the synthesis into a multicomponent procedure. This possibility relied on an attractive feature of some organometallic reagents: their addition to carbonyl compounds is generally slow.[9] Thus, we conceived that the conjugate addition of a suitable organometallic reagent, generated in situ from an organic bromide **2** (Barbier-like conditions), on dimethyl itaconate as the Michael acceptor could be the faster pathway. The resulting enolate would then add to the carbonyl compound **1** to induce the formation of a transient alcoholate,[10] which might undergo an intramolecular transesterification to provide the expected γ-butyrolactone **3**–**6**.



Scheme 1. Retrosynthetic scheme for the multicomponent synthesis of γ-butyrolactones.

A preliminary experiment, which was conducted in acetonitrile with benzaldehyde (**1a**), dimethyl itaconate, 4-bromoanisole (**2a**), cobalt(II) bromide as a catalyst and zinc dust as a reducer, indicated that the formation of the expected five-membered ring lactone **3a** was achievable in reasonable time and yield. This encouraging result prompted us to optimize the reaction conditions. Thus, in a first set

of experiments, we investigated the influence of several parameters, such as: temperature, dimethyl itaconate and cobalt bromide amounts, zinc dust activation method, and work-up conditions, on the reaction efficiency. To this end, 4-bromoanisole (**2a**; 1.5 equiv.) was allowed to react with dimethyl itaconate and benzaldehyde (**1a**; 1 equiv.) in the presence of zinc dust (4.6 equiv.) and cobalt bromide, in acetonitrile for 1–3 h;[11] the results are presented in Table 1.

Table 1. Optimization of the experimental conditions.[a]

1a **2a** **3a**

Entry	Itaconate amount [mmol]	$CoBr_2$ amount [mol-%][b]	Temp. [°C]	Zn dust activation[c]	Work-up[d]	Yield [%][e]
1	**15**	13	60	A	A	13
2	**30**	13	60	A	A	84
3	**50**	**13**	**60**	**A**	**A**	**95**
4	50	–	60	A	A	–
5	50	**6.5**	60	A	A	64
6	50	**100**	60	A	A	99
7	50	13	**20**	A	A	71
8	50	13	60	–	A	51
9	50	13	60	**B**	A	77
10	50	13	60	A	**B**	43

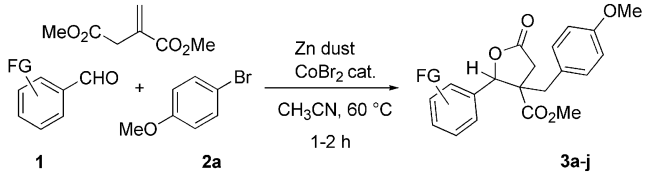
[a] *Reagents and conditions:* **2a** (2.7 g, 15 mmol), **1a** (1.1 g, 10 mmol), zinc dust (3 g, 46 mmol), acetonitrile (20 mL). [b] Calculated relative to **2a**. [c] Method A: TFA and $BrCH_2CH_2Br$; Method B: TFA and allyl chloride, see refs.[14b,14c] for details. [d] Method A: Filtration over Celite followed by chromatography over silica gel; Method B: Aqueous work-up followed by chromatography over silica gel. [e] Isolated yield.

These results indicate that the reaction works smoothly under a wide range of conditions. However, it should be mentioned that the use of an excess of dimethyl itaconate is crucial for the efficiency of the reaction (Table 1, entries 1–3).[12] The amount of cobalt(II) bromide can be raised to 100 mol-% (Table 1, entry 6) to induce quantitative formation of lactone **3a**. In contrast, lower amounts of $CoBr_2$ leads to a reduction in the reaction yield (Table 1, entry 5) and no coupling is observed in its absence (Table 1, entry 4), indicating its critical role in the process. Another interesting observation concerns the ability to complete the reaction at ambient temperature (Table 1, entry 7) with only a slight decrease of yield. This set of conditions constitute very reliable reaction parameters for syntheses involving heat-sensitive substrates. It can also be noted that the method of activation of zinc dust also plays a significant role. Indeed, the overall reaction is much more efficient under combined trifluoroacetic acid (TFA)/1,2-dibromoethane activation (Table 1, entry 3) than under TFA/allyl chloride activation (Table 1, entry 9) or without activation (Table 1, entry 8). The unexpected importance of the reaction workup conditions should also be noted; comparison of results reported in entries 3 and 10 of Table 1, for which the conditions only differed in a hydrolysis step, suggested that the lactone is water-sensitive.

Consequently, it appears that the most general and reliable conditions regarding the global efficiency of the reaction, both in terms of yield and atom economy, are those reported in entry 3 of Table 1. Standard reaction conditions thus involved acetonitrile as solvent, zinc dust (4.6 equiv., activated by using the joint assistance of TFA and 1,2-dibromoethane) as a reductive metal, $CoBr_2$ (13 mol-% vs. ArBr) as a catalyst, and the bromide (1.5 equiv.), the aldehyde (1 equiv.), and dimethyl itaconate (5 equiv.), reacting at 60 °C.

We then investigated the scope of the reaction system under these optimized conditions. In an initial series of experiments, dimethyl itaconate and 4-bromoanisole (**2a**), which were taken as model compounds, were allowed to react with a range of benzaldehyde derivatives for 1–2 h; the results are reported in Table 2.

Table 2. Scope of benzaldehyde derivatives.[a]



1 **2a** **3a-j**

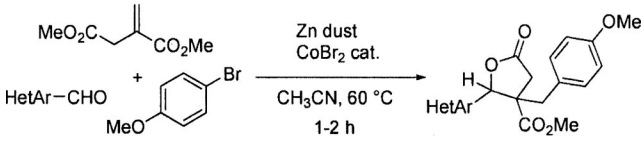
Entry	FG	3	Yield [%][b]
1	H	**3a**	95
2	4-OMe	**3b**	41
3	4-SMe	**3c**	51
4	4-Me	**3d**	68
5	3-Me	**3e**	79
6	2-Me	**3f**	71
7	3-Me, 4-Me	**3g**	61
8	4-F	**3h**	98
9	2-F	**3i**	42
10	2-CF_3	**3j**	56
11	4-CN		–[c]
12	4-NO_2		–

[a] *Reagents and conditions:* **2a** (2.7 g, 15 mmol), benzaldehyde derivative (10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), $CoBr_2$ (0.44 g, 2 mmol), acetonitrile (20 mL). [b] Isolated yield. [c] Degradation of the γ-butyrolactone upon chromatographic purification.

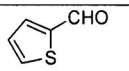
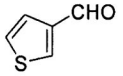
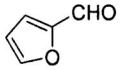
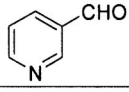
Yields generally range from moderate to excellent and it can be noted that the reaction tolerates a wide variety of functionalized aromatic aldehydes bearing, in particular, electron-donating groups and/or sterically hindering groups. In the case of *p*-cyanobenzaldehyde, degradation of the corresponding butyrolactone upon chromatographic purification did not allow the expected product to be isolated (Table 2, entry 11). It should be noted that a limitation of the process concerns the impossibility of employing nitro-containing aldehydes under such reductive conditions (Table 2, entry 12).

To extend the study, a range of heteroaromatic aldehydes were submitted to the reaction conditions; the results are summarized in Table 3.

Table 3. Scope of heteroaromatic aldehydes.[a]

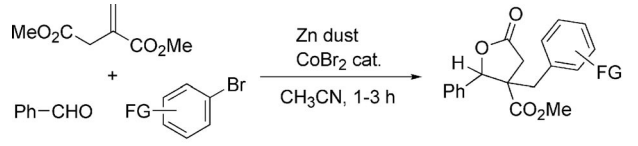


1 2a 4a-c

Entry	HetAr-CHO	4	Yield [%][b]
1		**4a**	75
2		**4b**	75
3		**4c**	49
4			–

[a] *Reagents and conditions:* **2a** (2.7 g, 15 mmol), heteroaromatic aldehyde (10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), $CoBr_2$ (0.44 g, 2 mmol), acetonitrile (20 mL). [b] Isolated yield.

Table 4. Scope of aryl bromides.[a]



1a 2 3a and 3k-u

Entry	FG	Temp. [°C]	3	Yield [%][b]
1	H	60	**3k**	64
2	4-OMe	60	**3a**	95
3	3-OMe	60	**3l**	44
4	2-OMe	60		–
5	2-OMe	25	**3m**	71[c]
6	4-SMe	60	**3n**	52
7	4-Me	60	**3o**	69
8	4-CF_3	60	**3p**	54
9	3-CF_3	60	**3q**	48
10	2-CF_3	60		–
11	2-CF_3	25	**3r**	55[c,d]
12	4-CO_2Me	60	**3s**	99
13	3-CO_2Me	60	**3t**	99
14	2-CO_2Me	60	**3u**	57
15	2-CO_2Me	25	**3u**	79[c]
16	2-CN	25		–[e]

[a] *Reagents and conditions:* Aryl bromide (15 mmol), **1a** (1.1 g, 10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), $CoBr_2$ (0.44 g, 2 mmol), acetonitrile (20 mL). [b] Isolated yield. [c] Reaction conducted with 100 mol-% $CoBr_2$. [d] The reaction time was 2 d. [e] No reaction.

The corresponding γ-butyrolactones were obtained in satisfactory to good yields, except when pyridine-3-carbaldehyde was used as starting material, for which no three-component coupling was observed even after 24 h heating at 60 °C (Table 3, entry 4). It can be noted that the major product of the reaction was the alcohol resulting from the direct addition of the organozinc onto the carbonyl function.

In a subsequent set of experiments, we examined the scope of aryl bromides; the results are reported in Table 4.

Very good yields were generally obtained with both electron-rich and electron-deficient aryl bromides. We were pleased to observe that even hindered aryl bromides underwent the coupling (Table 4, entries 5, 11, and 15). However, it should be noted that an adaptation to the procedure was required when starting from an *ortho*-substituted bromoarene. In this case, the reaction was conducted at room temperature to limit the formation of the biaryl, which resulted from the heat-promoted homocoupling of the starting halide. This assertion is illustrated by comparing the results presented in entries 4 and 5, 10 and 11, or 14 and 15 of Table 4. It should be noted that, in these cases, the presence of a large amount of cobalt bromide in the medium was crucial for the reaction to reach completion in reasonable times. In our opinion, this rather unexpected *ortho*-effect of the substituent is interesting from a synthetic point of view and would be worthy of further investigation.

Additional experiments were conducted starting from heteroaromatic bromides (bromopyridines, bromofurans, and bromothiophenes). Unfortunately, under the standard reaction conditions, these compounds did not undergo coupling. This inhibition of the reaction may be attributed to a possible poisoning of the catalyst by the heteroarene, thus preventing the formation of organometallic species and the overall associated process.

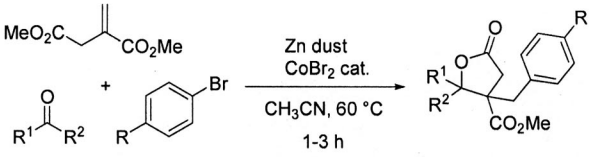
In further experiments, we undertook the three-component coupling starting from ketones; the results are presented in Table 5.

Although, as expected, the yields were generally lower than with aromatic aldehydes, it should be noticed that such couplings can provide rapid entry to some novel 2,2,3,3-tetrasubstituted γ-lactones bearing, in particular, a spiranic system (Table 5, entry 6).

We then examined the scope of the procedure further by conducting some additional experiments; the results are presented in Table 6.

An examination of these latter results, as well as those reported above, reveals that aromatic aldehydes may constitute the most suitable carbonyl compounds. Indeed, it can be seen that ketones (Table 5) are less reactive than benzaldehyde derivatives (Table 2). Furthermore, other carbonyl compounds, such as aliphatic aldehydes (Table 6, entry 1), paraformaldehyde (Table 6, entry 2), or ethyl glyoxylate (Table 6, entry 3) are either less efficient in the coupling or not reactive at all. Benzyl bromide did not undergo the coupling, even in the presence of additional cobalt bromide (Table 6, entry 4). On the other hand, vinylic bromide is almost as reactive as an aryl bromide, furnishing the corresponding lactone in reasonable time and yield (Table 6, entry 5).

Table 5. Scope of carbonyl compounds.[a]



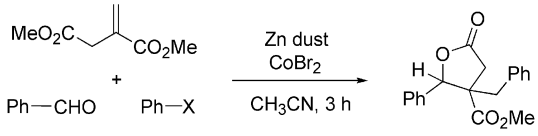
1 2 5a-e

Entry	Ketone	R	5	Yield [%][b]
1		OMe		-
2		OMe	**5a**	54
3		OMe	**5b**	85
4		H	**5c**	52
5		H	**5d**	66
6		H	**5e**	14

[a] *Reagents and conditions:* Aryl bromide (15 mmol), carbonyl compound **1** (10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), $CoBr_2$ (0.44 g, 2 mmol), acetonitrile (20 mL). [b] Isolated yield.

We also investigated the influence of the halogen atom connected to the phenyl moiety; the results are reported in Table 7.

Table 7. Effect of the halogen atom connected to the phenyl moiety.[a]

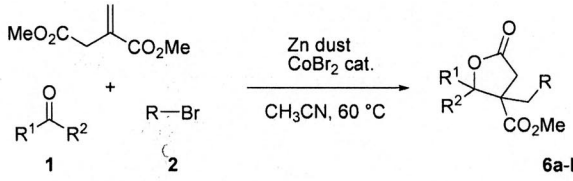


1a 3k

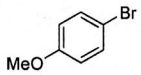
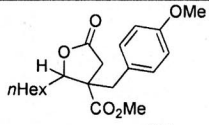
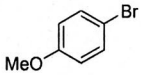
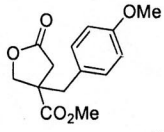
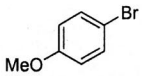
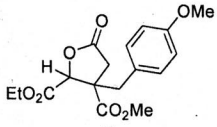
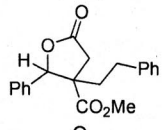
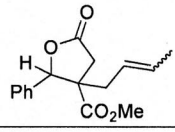
Entry	Halogen X	Temp. [°C]	$CoBr_2$[b]	Yield [%][c]
1	I	60	13 mol-%	40
2	I	20	13 mol-%	45
3	I	60	–	–
4	Br	60	13 mol-%	64
5	Cl	60	13 mol-%	–
6	Cl	60	100 mol-%	–

[a] *Reagents and conditions:* Halobenzene (2.26 g, 15 mmol), **1a** (1.1 g, 10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), acetonitrile (20 mL). [b] The amount of $CoBr_2$ is calculated relative to the halobenzene. [c] Isolated yield.

Table 6. Miscellaneous experiments.[a]



1 2 6a-b

Entry	Carbonyl compound	RBr	Time [h]	Product	6	Yield [%][b]
1			0.75		**6a**	27
2	$-(CH_2O)_n-$		3			-
3			6			-
4			8			-
5			2.5		**6b**	56[c]

[a] *Reagents and conditions:* Organic bromide **2** (15 mmol), carbonyl compound **1** (10 mmol), dimethyl itaconate (7.9 g, 50 mmol), zinc dust (3 g, 46 mmol), $CoBr_2$ (0.44 g, 2 mmol), acetonitrile (20 mL). [b] Isolated yield. [c] ***Caution!*** The vigorous reaction was conducted without activation of the zinc dust.

It should be noted that iodobenzene was almost as efficient as bromobenzene in the coupling reaction, even at room temperature (Table 7, entry 2), albeit in the required presence of cobalt bromide (Table 7, entry 3). On the other hand, chlorobenzene did not undergo the reaction, even in the presence of increased amounts of cobalt bromide (Table 7, entry 6). Taken together, these results indicate that bromoarenes constitute very reliable starting halides, both in terms of reactivity, commercial availability and price.

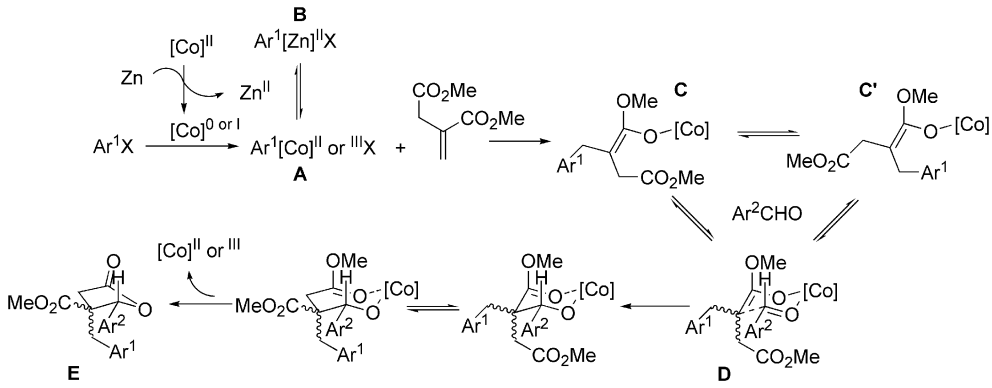
The efficiency of catalysts other than $CoBr_2$ was also assessed. Inferior results were obtained by using $CoBr_2$bpy instead of $CoBr_2$, and nickel-based catalysts such as $NiBr_2$ or $NiBr_2$bpy were also inefficient in the process.

In previous papers dealing with the Mannich-like, three-component coupling of organozinc reagents with aldehydes and amines,[13] the crucial role of the solvent in the reaction efficiency was recognized. In particular, it was noticed that common solvents such as tetrahydrofuran (THF) can dramatically slow down the reaction rate, probably by stabilizing the organozinc reagent. Hence, we chose to also investigate the influence of THF on the present reaction. To this end, we replaced acetonitrile with THF in the Barbier-like procedure; preliminary experiments resulted in failure, with no coupling products being detected in the reaction mixture. This result is consistent with previous works by Gosmini[14] that indicated that the zinc dust/cobalt bromide system is able to activate aryl halides and produce organometallic reagents, provided that the reaction is conducted in acetonitrile. Consequently, the effect of THF was assessed by using preformed[15] or commercial[16] organozinc reagents. Thus, organozinc reagents were allowed to react with benzaldehyde (**1a**) and dimethyl itaconate for 24 h at 60 °C. These experiments indicated that although the reaction can be conducted in acetonitrile to furnish the expected lactone in moderate yield (48%), no coupling products are observed in the presence of THF, even when the reaction involves organozinc that was preformed in acetonitrile. Further addition of cobalt bromide into the reaction mixture did not result in improved couplings, which supports the probable inhibitory role of THF in the present process.

Reaction Mechanism

Additional experiments were devised to examine the reaction mechanism. Preliminary experiments revealed that organozinc reagents, preformed in acetonitrile, can be employed in the reaction, hence suggesting that these organometallics might be nucleophilic initiators of the domino process. However, the requisite presence of cobalt bromide in the reaction medium during the arylzinc synthesis step also implies the continuous presence of transient organocobalt species that might also play additional roles in the following three-component coupling reaction. In addition, control experiments revealed that the presence of cobalt bromide was essential (Table 1, entry 4 and Table 7, entry 3). We then planed to replace the zinc dust by other reducing metals in order to evaluate their activity as initiators of the domino process. These experiments, which were conducted with a range of metallic powders (Sn, Fe, Cr, Mn, Al, and Mg), indicated that although most metals were unable to initiate the reaction, manganese powder constituted a very convenient reducing agent that was almost as efficient as zinc dust.

On the basis of these results, a reaction mechanism can be proposed. The first point to note concerns the possibility of conducting the reaction with reducers other than zinc dust, which indicates that the formation of an organozinc compound is not required for the reaction to proceed. The use of manganese as a suitable reducer of cobalt bromide has been described previously by Gosmini and co-workers in a study on the conjugate addition of aryl halides onto activated olefins.[17] The authors mention the potential formation of an arylcobalt species that can react with an electrophilic olefin to produce a cobalt enolate, which can be further protonated in situ by water. Consequently, we assume that an organocobalt compound **A** could also be the key intermediate in this process. Such a species could favor conjugate addition and the further aldolization–cyclization process leading to the formation of the five-membered ring lactone, as depicted in Scheme 2, with Zn as the reducing metal.



Scheme 2. Proposed mechanism for the metalation/conjugate addition/aldolization/cyclization process.

Several additional observations support such a cobalt-mediated process. The first point concerns the fact that the reaction is much more efficient under Barbier-like conditions than with preformed arylzinc reagents. In the latter case, it is assumed that the reaction mechanism involves the formation of an intermediate organocobalt species **A**, which is entirely converted into the corresponding organozinc **B** by a thermodynamically favored transmetalation.[18] Consequently, the first observation accounts for the limited reactivity of the organozinc species towards Michael acceptors, and the reverse transmetalation into the corresponding organocobalt species **A** must be necessary for the reaction to take place. Additionally, the existence of a transmetalation equilibrium between the organozinc **B** and the organocobalt **A** is supported by the observation that the reaction yield increases with increasing amounts of cobalt bromide (Table 1, entries 3, 4, 5, and 6), thus revealing that a plausible cobalt-promoted equilibrium shift to the reactive organometallic species **A** may occur. Under Barbier-like conditions, the organocobalt species that is primarily formed in the medium might continuously trap dimethyl itaconate to produce the cobalt enolate (**C** and **C′** mixture) instead of undergoing a transmetalation into the inactive organozinc species. Undoubtedly, this would favor the subsequent domino process that leads to the final formation of lactone **E**. On the basis of this proposed mechanism, one could also imagine potential roles of THF that might substantially decrease the overall reaction rate by, for example, preventing transmetallation from **B** to **A** and/or limiting the reactivity of the organocobalt species **A** by chelation to the cobalt atom.

The stereochemical outcome of the reaction was characterized by a lack of selectivity; the diastereoisomeric ratio, determined by GC analyses, was generally between 60:40 and 50:50. It is assumed that the stereoselectivity of the aldol reaction is defined by the configuration of the enolate in the Zimmerman–Traxler transition state **D**. In the present case, the almost identical steric bulk of both $-CH_2Ar^1$ and $-CH_2CO_2Me$ would not permit a notable predominance of the *Z* or *E* enolate in the medium, thus giving rise to the formation of the corresponding aldol coupling products in similar ratios. Further efforts will be directed toward the design of reaction systems that provide a substantial improvement of diastereoselectivities.

Crystallographic Analyses

For all experiments conducted with a benzaldehyde derivative as the starting carbonyl compound, the cyclic character of the final product was unambiguously determined by using NMR analysis and, in particular, HMBC experiments, which revealed a scalar correlation between the carbon of the carbonyl and the proton linked to the benzylic carbon ($^3J_{CH}$). However, an X-ray diffraction experiment confirming the nature of the final product was realized with a single crystal of compound **3q** (Figure 1).

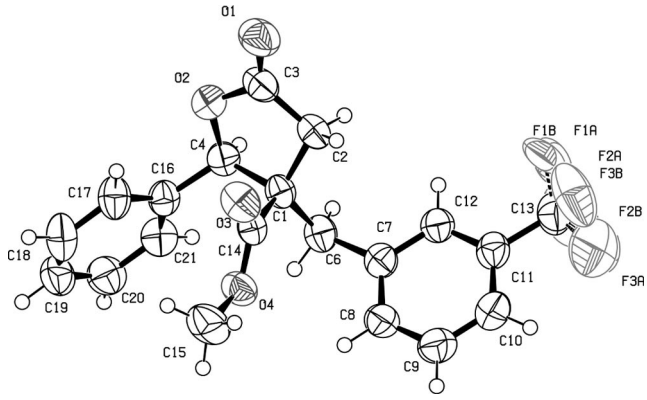


Figure 1. ORTEP drawing for compound **3q**.

Starting from ketones, the absence of a benzylic proton on the coupling product made NMR determination of the structure difficult. Thus, single-crystal X-ray analysis was also recorded for a diastereoisomer of compound **5b**, which also revealed the cyclic character of the molecule (Figure 2).

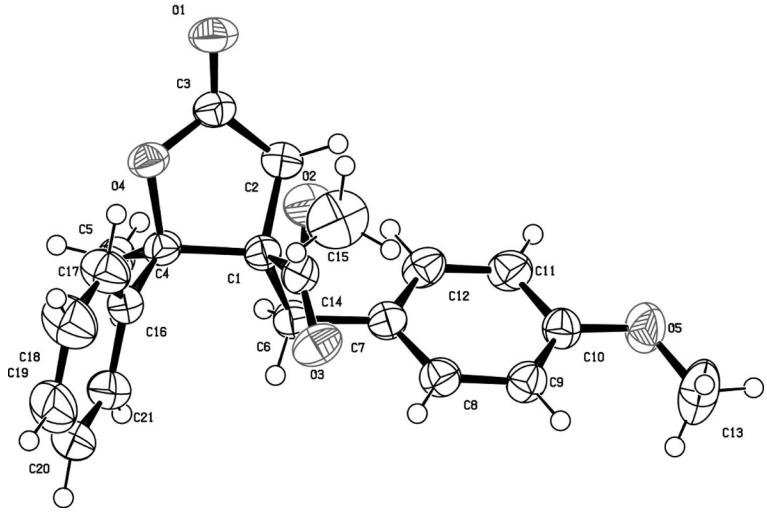


Figure 2. ORTEP drawing for compound **5b**.

Conclusions

In conclusion, we have demonstrated that novel 2,3-di- and 2,2,3-trisubstituted 3-methoxycarbonyl-γ-butyrolactones can be successfully obtained through a simple and efficient, one-pot, three-component reaction between dimethyl itaconate, aryl bromides, and carbonyl compounds. The domino process, which involves the formation of an organometallic reagent, a conjugate addition, an aldol coupling, and a final cyclization in the same experimental step, provides potential access to an important variety of γ-butyrolactones derived from paraconic acid, making this strategy suitable for parallel synthesis. The development of intramolecular versions of this reaction is in progress.

Experimental Section

General Procedure for the Synthesis of Lactones: A dried 100-mL round-bottomed flask was flushed with argon and charged with acetonitrile (20 mL). Dodecane (0.2 mL), zinc dust (3 g, 46 mmol), dimethyl itaconate (7.9 g, 50 mmol), aromatic aldehyde (10 mmol), and aryl bromide (15 mmol) were added whilst stirring. Cobalt bromide (0.44 g, 2 mmol), trifluoroacetic acid (0.1 mL), and 1,2-dibromoethane (0.2 mL) were added successively to the mixture, which was heated at 60 °C until consumption of the aryl bromide was complete (45 min to 3 h, monitored by gas chromatography). The reaction mixture was then filtered through Celite. The Celite was washed several times with diethyl ether and the combined organic fractions were concentrated in vacuo. The crude reaction product was purified by flash column chromatography over silica gel (pentane/diethyl ether, 1:0 to 0:1) to afford the lactone.

CCDC-753629 [for *rac*-**5b**, (*RR*/*SS*)] and -753630 [for *rac*-**3q**, (*RR*/*SS*)] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): General experimental procedures, characterization data and copies of NMR spectra for all compounds.

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