Multicomponent synthesis of polysubstituted γ-butyrolactones under Barbier-like conditions*

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Abstract: The one-pot, three-component synthesis of 2,3-di- and 2,2,3-trisubstituted-3-methoxycarbonyl-γ-butyrolactones starting from aryl bromides, dimethyl itaconate, and aldehydes or ketones is described. The cobalt-catalyzed domino process formally involves the in situ metallation of an aromatic bromide, a conjugate addition onto dimethyl itaconate, an aldolization reaction with a carbonyl compound, and a final cyclization into a five-membered ring lactone. This procedure is applied to the concise synthesis of a range of polyfunctionalized γ-butyrolactones displaying a paraconic acid methyl ester subunit.

Keywords: cobalt; domino process; lactones; multicomponent reactions; zinc.

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 both display antitumor and antibiotic biological activities, but also represent convenient building blocks in the synthesis of natural compounds of pharmaceutical interest [3]. While these interesting properties have made them attractive synthetic targets for the organic chemist [4], the preparation of 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 metallation–conjugate addition–aldol coupling–cyclization process [8]. It was noticed that the cobalt bromide/zinc dust association constitutes a very convenient reducing system for the in situ formation of aromatic organometallic species, prone to undergo a conjugate addition onto dimethyl itaconate and to initiate the subsequent domino process. In the present 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. We also discuss a putative reaction pathway.

RESULTS AND DISCUSSION

As a starting point of the study, we anticipated that a range of 2,3-polysubstituted paraconic esters bearing a functionalized benzyl group at the 3 position should be accessible through a sequence involving the successive formation of three single bonds: (1) a conjugate addition, (2) an aldol reaction, (3) a cyclization (Scheme 1). We also considered the additional opportunity to turn the synthesis to a multicomponent procedure. This possibility was relying on an attractive feature of some organometallic reagents: their addition to carbonyl compounds is generally slow [9]. Thus, we conceived that under proper catalytic conditions, the conjugate addition of a suitable organometallic reagent, generated in situ from an aryl 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 **3–4**.
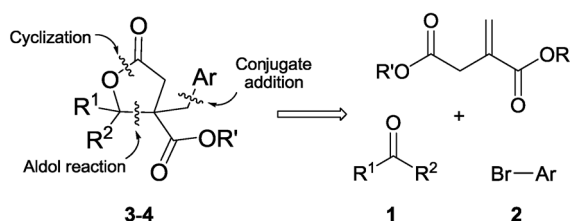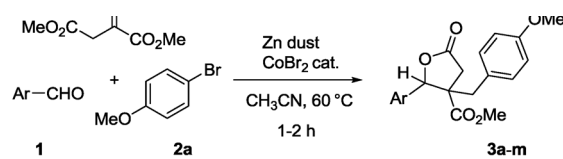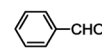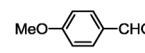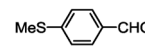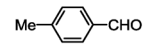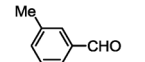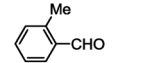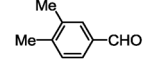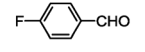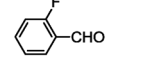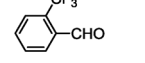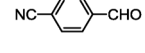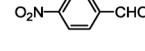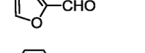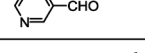

Scheme 1 Retrosynthetic scheme for the multicomponent synthesis of γ-butyrolactones.

A preliminary experiment, attempted in acetonitrile with benzaldehyde **1a**, dimethyl itaconate, 4-bromoanisole **2a**, cobalt 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. Most general and reliable settings, regarding the global efficiency of the reaction, both in terms of yield and atom economy, were thus defined as follows: acetonitrile is used as a solvent, zinc dust (4.6 equiv, activated by using the joined 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) are allowed to react at 60 °C.

We then started investigating the scope of this reaction system under these optimized conditions. In a first series of experiments, dimethyl itaconate and 4-bromoanisole **2a**, taken as model compounds, were allowed to react with a range of aromatic and heteroaromatic aldehydes for 1–2 h [11]. Results are reported in Table 1.

Yields generally range from moderate to excellent, and it can be noted that the reaction tolerates an important variety of functionalized aromatic aldehydes bearing, in particular, electron-donating groups and/or -hindering groups. In the case of the *p*-cyanobenzaldehyde, the degradation of corresponding butyrolactone upon chromatographic purification did not allow the isolation of the expected product (Table 1, entry 11). Moreover, it can be noticed that a limitation of the process concerns the impossibility of employing nitro-containing aldehydes under such reductive conditions (Tab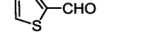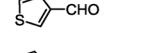le 1, entry 12). Starting from heteroaromatic aldehydes, the corresponding γ-butyrolactones are obtained in satisfactory to good yields except with 3-pyridine carboxaldehyde for which no three-component coupling is observed, even after 24 h heating at 60 °C (Table 1, entry 16). It can be noted that the major product of the reaction is the alcohol resulting from the direct addition of the organozinc onto the carbonyl function.

Table 1 Scope of aldehyde derivatives[a].

Entry	Ar-CHO	3	Yield [%][b]
1	⬡–CHO	3a	95
2	MeO–⬡–CHO	3b	41
3	MeS–⬡–CHO	3c	51
4	Me–⬡–CHO	3d	68
5	(3-Me)⬡–CHO	3e	79
6	(2-Me)⬡–CHO	3f	71
7	(2,3-Me2)⬡–CHO	3g	61
8	F–⬡–CHO	3h	98
9	(2-F)⬡–CHO	3i	42
10	(2-CF3)⬡–CHO	3j	56
11	NC–⬡–CHO		–[c]
12	O2N–⬡–CHO		–
13	(thiophene-2)–CHO	3k	75
14	(thiophene-3)–CHO	3l	75
15	(furan-2)–CHO	3m	49
16	(pyridine)–CHO		–

[a] All experiments were conducted with 20 mL of acetonitrile, 2.7 g (15 mmol) of bromoanisole **2a**, 10 mmol of the aldehyde, 7.9 g (50 mmol) of dimethyl itaconate, 3 g (46 mmol) of zinc dust, 0.44 g (2 mmol) of CoBr₂. [b] Isolated yield. [c] Degradation of the γ-butyrolactone upon chromatographic purification.

In a few more experiments, we undertook to realize three-component couplings starting from ketones. Results are presented in Table 2.

Table 2 Scope of carbonyl compounds[a].

Entry	Ketone	R	4	Yield [%][b]
1	Ph Ph (O)	OMe		-
2	Ph CF₃ (O)	OMe	4a	54
3	Ph Me (O)	OMe	4b	85
4	Ph Et (O)	H	4c	52
5	Me Me (O)	H	4d	66
6	(cyclohexanone)	H	4e	14

[a] All experiments were conducted with 20 mL of acetonitrile, 15 mmol of the aryl bromide, 10 mmol of the carbonyl compound **1**, 7.9 g (50 mmol) of dimethyl itaconate, 3 g (46 mmol) of zinc dust, 0.44 g (2 mmol) of $CoBr_2$. [b] Isolated yield.

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

In the following set of experiments, we examined the scope of aryl bromides. Results are reported in Table 3.

Very good yields are generally obtained with both electron-rich and -deficient aryl bromides. We were satisfied to observe that even hindered aryl bromides can undergo the coupling (Table 3, entries 5, 11, and 15). However, it can be noted that an experimental adaptation of the procedure was required when starting from an ortho-substituted bromoarene. In that case, the reaction was conducted at room temperature in order to ensure a limited formation of the biaryle, resulting from the heat-promoted homocoupling of the starting halide. This assertion was illustrated by the comparison of the results presented in entries 4 and 5, 10 and 11, or 14 and 15 of Table 3. It can be noted that in these cases, the presence of an important amount of cobalt bromide in the medium was crucial for the completion of the reaction in reasonable times. To our opinion, this rather unexpected ortho-effect of the substituent is interesting from a synthetic point of view and would worth being further investigated.

Table 3 Scope of aryl bromides[a].

Entry	FG =	Temperature [°C]	3	Yield [%][b]
1	H	60	**3n**	64
2	4-OMe	60	**3a**	95
3	3-OMe	60	**3o**	44
4	2-OMe	60		-
5	2-OMe	25	**3p**	71[c]
6	4-SMe	60	**3q**	52
7	4-Me	60	**3r**	69
8	4-CF$_3$	60	**3s**	54
9	3-CF$_3$	60	**3t**	48
10	2-CF$_3$	60		-
11	2-CF$_3$	25	**3u**	55[c],[d]
12	4-CO$_2$Me	60	**3v**	99
13	3-CO$_2$Me	60	**3w**	99
14	2-CO$_2$Me	60	**3x**	57
15	2-CO$_2$Me	25	**3x**	79[c]
16	2-CN	25		-[e]

[a] All experiments were conducted with 20 mL of acetonitrile, 15 mmol of the aryl bromide, 1.1 g (10 mmol) of benzaldehyde **1a**, 7.9 g (50 mmol) of dimethyl itaconate, 3 g (46 mmol) of zinc dust, 0.44 g (2 mmol) of CoBr$_2$. [b] Isolated yield. [c] Reaction conducted with a 100 mol% CoBr$_2$ amount. [d] The reaction time was 2 days. [e] No reaction.

Additional experiments were conducted starting from heteroaromatic bromides (bromopyridines, bromofuranes, and bromothiophenes). Unfortunately, in standard reaction conditions, these compounds do not undergo the 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 another series of experiments, it was investigated the influence of the nature of the halogen atom connected to the phenyl moiety. It could be noticed that iodobenzene is mostly as efficient as bromobenzene in the coupling, even at room temperature, albeit in the required presence of cobalt bromide. On the other hand, chlorobenzene does not undergo the reaction, even in the presence of increased amounts of cobalt bromide. Put together, these results mainly indicate that bromoarenes constitute very reliable starting halides, both in terms of reactivity, commercial availability, and price. The efficiency of some catalysts other than CoBr$_2$ was also assessed. Worse results were obtained by using CoBr$_2$bpy instead of CoBr$_2$. Some other experiments indicated that nickel-based catalysts like NiBr$_2$ or NiBr$_2$bpy are inefficient in the process.
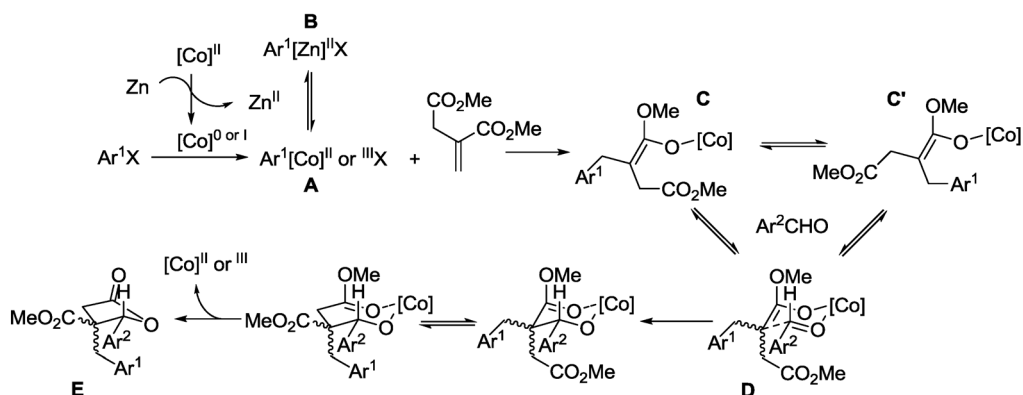
Reaction mechanism

In previous papers dealing with the Mannich-like three-component coupling of organozinc reagents with aldehydes and amines [12], it was pointed out the crucial role of the solvent over the reaction efficiency. In particular, it was noticed that a prevalent solvent like 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 over the present reaction. In this aim, we tried to replace acetonitrile by THF in the Barbier-like procedure. Preliminary experiments resulted in failures, no coupling products being detected in the reaction mixture. This result is consistent with previous works of Gosmini [13], indicating 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, it was chosen to assess the effect of THF by operating from preformed [14] or commercial [15] organozinc reagents. Thus, organozinc reagents were allowed to react with benzaldehyde **1a** and dimethyl itaconate for a 24 h at 60 °C. These experiments indicated that while 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 starting from organozinc preformed in acetonitrile. The further addition of cobalt bromide in the reaction mixture did not result in improved couplings, thus confirming the probable inhibitory role of THF over the present process.

Some additional experiments were dedicated to the examination of the reaction mechanism. Preliminary experiments had 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 during the following three-component coupling reaction. In addition, some experiments had revealed that the presence of cobalt bromide was compulsory. We then planned to replace zinc dust by other reducing metals in order to evaluate their activity as initiators of the domino process. These experiments, which were realized with a range of metallic powders (Sn, Fe, Cr, Mn, Al, Mg), indicated that although most metals are unable to initiate the reaction, manganese powder constitutes a very convenient reducing agent, 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 operating with a reducer other than zinc dust, indicating that the formation of an organozinc compound is not required for the reaction to proceed. The utilization of manganese as a suitable reducer of cobalt bromide has been previously described by Gosmini and co-workers in a study dedicated to the conjugate addition of aryl halides onto activated olefins [16]. The authors mention the potential formation of an arylcobalt species, whose reaction with an electrophilic olefin leads to the production of a cobalt enolate, which can be further protonated in situ by water. Consequently, we assume that an organocobalt compound **A** can also be the key intermediate of the herein-mentioned process. This species could favor a conjugate addition and the further aldolization–cyclization process leading to the formation of the five-membered ring lactone, as depicted in Scheme 2, with zinc as the reducing metal.

Additionally, several additional observations account for such a cobalt-mediated process. The first point to note 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 transmetallation [17]. Consequently, the first observation accounts for a limited reactivity of the organozinc species towards Michael acceptors, and the reverse transmetallation into the corresponding organocobalt species **A** should be necessary for the reaction to take place. Additionally, the existence of a transmetallation equilibrium between the organozinc **B** and the organocobalt **A** is ascertained by some experiments, indicating that the reaction yield increases concomitantly with the rise of the cobalt bromide amount, thus revealing a plausible

Scheme 2 Proposal for the mechanism of the metallation-conjugate addition–aldolization–cyclization process.

cobalt-promoted equilibrium shifting to the reactive organometallic species **A**. 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 transmetallation into the inactive organozinc species. Undoubtedly, this should favor the subsequent domino process that leads to the final formation of the lactone **E**. On the basis of this mechanism proposal, one could also imagine potential roles of THF which might substantially decrease the overall reaction rate by, e.g., preventing transmetallation from **B** to **A** and/or limiting the reactivity of the organocobalt **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 gas chromatography (GC) analyses, being generally comprised between 60/40 and 50/50. It is well 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 similar steric hindrance 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. Consequently, further efforts will be directed toward design of reaction systems prone to providing a substantial improvement of diastereoselectivities.

Crystallographic analyses

For all the experiments realized with a benzaldehyde derivative as the starting carbonyl compound, the cyclic character of the final product was unambiguously determined using NMR, and, in particular, heteronuclear multiple-bond correlation (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** (Fig. 1).
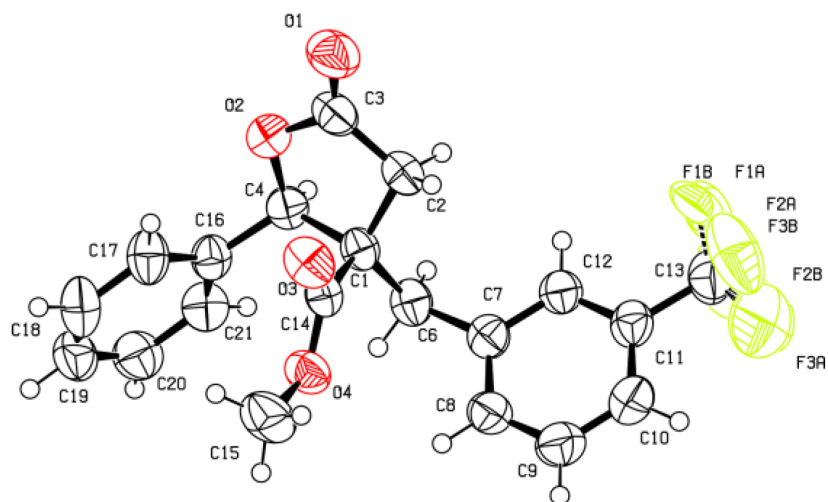
Fig. 1 ORTEP drawing for compound **3q**.

Starting from ketones, the absence of benzylic proton on the coupling product implied a more harsh NMR determination of the structures. Thus, a single-crystal X-ray analysis was also recorded for a diastereoisomer of compound **5b**, also revealing the cyclic character of the molecule (Fig. 2).
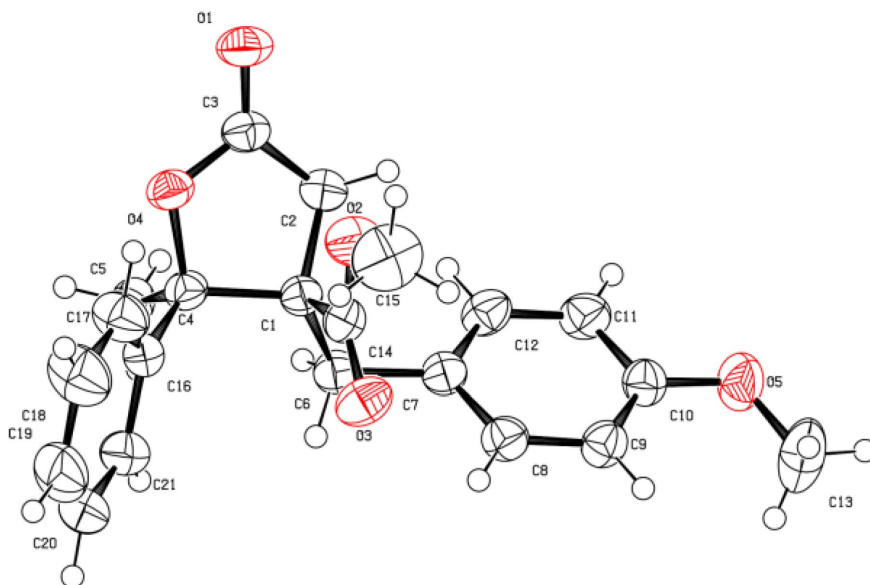

Fig. 2 ORTEP drawing for compound **5b**.

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 in the same experimental step the formation of an organometallic reagent, a conjugate addition, an aldol coupling, and a final cyclization, provides a potential access to a rather important variety of γ-butyrolactones derived from paraconic acid, making this strategy suitable for parallel synthesis. The extension of the reaction to polyfunctional substrates is currently under progress.

EXPERIMENTAL SECTION

General procedure for the synthesis of lactones: A dried 100-ml round-bottom 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 under 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 complete consumption of the aryl bromide (45 min to 3 h, monitored by GC). The reaction mixture was then filtered through celite. Celite was washed several times with diethyl ether, and the combined organic fractions were concentrated in vacuo. The crude reaction product was purified via flash column chromatography over silica gel using a pentane/diethyl ether mixture (1:0 to 0:1) as an eluant to afford the five-membered ring lactone.

CRYSTALLOGRAPHIC STRUCTURES

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-753629 [racemic compound **5b**, (*RR/SS*)] and CCDC-753630 [racemic compound **3q**, (*RR/SS*)]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

ACKNOWLEDGMENTS

REFERENCES

1. (a) H. M. R. Hoffmann, J. Rabe. *Angew. Chem., Int. Ed.* **24**, 94 (1985); (b) O. Spring, K. Albert, W. Gradmann. *Phytochemistry* **20**, 1883 (1981); (c) N. H. Fischer, T. Lu, C. L. Cantrell, J. Castaneda-Acosta, L. Quijano, S. Franzblau. *Phytochemistry* **49**, 559 (1998); (d) T.-C. Wang, K.-H. Lee, Y.-L. Chen, S.-S. Liou, C.-C. Tzeng. *Bioorg. Med. Chem. Lett.* **8**, 2773 (1998); (e) A. Ortega, R. A. Toscano, E. Maldonado. *Phytochemistry* **49**, 1085 (1998); (f) Y. Higuchi, F. Shimoma, M. Ando. *J. Nat. Prod.* **66**, 810 (2003); (g) K.-H. Lee, I. H. Hall, E. C. Mar, C. O. Starnes, S. A. Elgebaly, T. G. Waddell, R. I. Hadgraft, C. G. Ruffner, I. Weidner. *Science* **196**, 533 (1977); (h) R. Romagnoli, P. G. Baraldi, M. A. Tabrizi, J. Bermejo, F. Estévez, M. Borgatti, R. Gambari. *J. Med. Chem.* **48**, 7906 (2005); (i) M. A. Hughes, J. M. McFadden, C. A. Townsend. *Bioorg. Med. Chem. Lett.* **15**, 3857 (2005); (j) R. da Silva, G. H. B. de Souza, A. A. da Silva, V. A. de Souza, A. C. Pereira, V. de A. Royo, M. L. A. de Silva, P. M. Donate, A. L. S. de Matos Araújo, J. C. T. Carvalho, J. K. Bastos. *Bioorg. Med. Chem. Lett.* **15**, 1033 (2005); (k) N. Petragnani, H. M. C. Ferraz, G. V. J. Silva. *Synthesis* 157 (1986).

2. (a) M. Pohmakotr, W. Harnying, P. Tuchinda, V. Reutrakul. *Helv. Chim. Acta* **85**, 3792 (2002); (b) M. T. Barros, C. D. Maycock, R. M. Ventura. *Org. Lett.* **5**, 4097 (2003); (c) D. Blanc, J. Madec, F. Popowyck, T. Ayad, P. Phansavath, V. Ratovelomanana, J.-P. Genêt. *Adv. Synth. Catal.* **349**, 943 (2007); (d) S. Bazin, L. Feray, N. Vanthuyne, D. Siri, M. P. Bertrand. *Tetrahedron* **63**, 77 (2007); (e) C. Forzato, G. Furlan, P. Nitti, G. Pitacco, E. Valentin, E. Zangrando, P. Buzzini, M. Goretti, B. Turchetti. *Tetrahedron: Asymmetry* **19**, 2026 (2008); (f) X. Huang, X. Chen Y. Chen, A. Zhang, X. Li. *Tetrahedron: Asymmetry* **19**, 2529 (2008); (g) F. Berti, C. Forzato, G. Furlan, P. Nitti, G. Pitacco, E. Valentin, E. Zangrando. *Tetrahedron: Asymmetry* **20**, 313 (2009); (h) S. Coriani, C. Forzato, G. Furlan, P. Nitti, G. Pitacco, M. Ringholm, K. Ruud. *Tetrahedron: Asymmetry* **20**, 1459 (2009); (i) D. Horhant, A.-C. Le Lamer, J. Boustie, P. Uriac, N. Gouault. *Tetrahedron Lett.* **48**, 6031 (2007); (j) H.-C. Kim, O.-S. Park. *Tetrahedron: Asymmetry* **19**, 896 (2008); (k) M. Amador, X. Ariza, J. Garcia, J. Ortiz. *J. Org. Chem* **69**, 8172 (2004); (l) A. Brecht-Forster, J. Fitremann, P. Renaud. *Helv. Chim. Acta* **85**, 3965 (2002); for a recent review on the synthesis of paraconic acids, see: (m) R. Bandichhor, B. Nosse, O. Reiser. *Top. Curr. Chem.* **243**, 43 (2005).

3. (a) S. B. Mahato, K. A. I. Siddiqui, G. Battacharya, T. Ghosal, K. Miyahara, M. Sholichin, T. Kawasaki. *J. Nat. Prod.* **50**, 245 (1987); (b) M. M. Murta, M. B. M. De Azevedo, A. E. Greene. *J. Org. Chem.* **58**, 7537 (1993); (c) P. A. Jacobi, P. Herradura. *Tetrahedron Lett.* **37**, 8297 (1996); (d) B. K. Park, M. Nakagawa, A. Hirota, M. Nakayama. *J. Antibiot.* **41**, 751 (1988); (e) M. S. Maier, D. I. G. Marimon, C. A. Stortz, M. T. Alder. *J. Nat. Prod.* **62**, 1565 (1999); (f) X. Ariza, J. Garcia, M. Lopez, L. Montserrat. *Synlett* 120 (2001); (g) C. Böhm, O. Reiser. *Org. Lett.* **3**, 1315 (2001); (h) K. Müller. *Appl. Microbiol. Biotechnol.* **56**, 9 (2001).

4. (a) F. Berti, F. Felluga, C. Forzato, G. Furlan, P. Nitti, G. Pitacco, E. Valentin, M. T. Barros. *Tetrahedron: Asymmetry* **17**, 2344 (2006); (b) A. M. Jacobine, W. Lin, B. Walls, C. K. Zercher. *J. Org. Chem.* **73**, 7409 (2008); (c) S. S. Sohn, E. L. Rosen, J. W. Bode. *J. Am. Chem. Soc.* **126**, 14370 (2004); (d) Y. Li, Z.-A. Zhao, H. He, S.-L. You. *Adv. Synth. Catal.* **350**, 1885 (2008); (e) S. N. Greszler, J. S. Johnson. *Angew. Chem., Int. Ed.* **48**, 3689 (2009); (f) T. H. Mäkelä, S. A. Kaltia, K. T. Wähälä, T. A. Hase. *Steroids* **66**, 777 (2001); (g) R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor. *Angew. Chem., Int. Ed.* **48**, 9426 (2009); (h) T. Shono, H. Hamaguchi, I. Nishiguchi, M. Sasaki, T. Miyamoto, M. Miyamoto, S. Fujita. *Chem. Lett.* 1217 (1981); (i) F. D'Onofrio, R. Margarita, L. Parlanti, G. Piancatelli, M. Sbraga. *Chem. Commun.* 185 (1998); (j) A. Méou, L. Lamarque, P. Brun. *Tetrahedron Lett.* **43**, 5301 (2002).

5. J. Zhu, H. Bienaymé. In *Multicomponent Reactions*, Wiley-VCH, Weinheim (2005).

6. For recent reviews on multicomponent reactions (MCRs) and asymmetric MCRs (AMCRs), see: (a) R. V. A. Orru, M. De Greef. *Synthesis* 1471 (2003); (b) J. Zhu. *Eur. J. Org. Chem.* 1133 (2003); (c) C. Hulme, V. Gore. *Curr. Med. Chem.* **10**, 51 (2003); (d) G. Balme, E. Bossharth, N. Monteiro. *Eur. J. Org. Chem.* 4101 (2003); (e) C. Simon, T. Constantieux, J. Rodriguez. *Eur. J. Org. Chem.* 4957 (2004); (f) A. Dömling. *Chem. Rev.* **106**, 17 (2006); (g) D. M. D'Souza, T. J. J. Müller. *Chem. Soc. Rev.* **36**, 1095 (2007); (h) N. Isambert, R. Lavilla. *Chem.—Eur. J.* **14**, 8444 (2008); (i) B. A. Arndtsen. *Chem.—Eur. J.* **15**, 302 (2009); (j) G. Guillena, D. J. Ramón, M. Yus. *Tetrahedron: Asymmetry* **18**, 693 (2007); (k) D. J. Ramón, M. Yus. *Angew. Chem., Int. Ed.* **44**, 1602 (2005); (l) A. Dömling, I. Ugi. *Angew. Chem., Int. Ed.* **39**, 3168 (2000).

7. The synthesis of *N*-carbamoylmethyl-α-aminobutyrolactones by the Ugi MCR has been reported, see: (a) S. J. Park, G. Keum, S. B. Kang, H. Y. Koh, Y. Kim. *Tetrahedron Lett.* **39**, 7109 (1998); for the synthesis of α-methylene-γ-butyrolactones starting from preformed alkylcopper reagents, Michael acceptors, iodomethylzinc iodide, and aldehydes, see: (b) A. Sidduri, P. Knochel. *J. Am. Chem. Soc.* **114**, 7579 (1992).

8. C. Le Floch, C. Bughin, E. Le Gall, E. Léonel, T. Martens. *Tetrahedron Lett.* **50**, 5456 (2009).

9. For instance, arylzinc reagents obtained using the $CoBr_2$/Zn system do not react rapidly with aromatic aldehydes.

10. A related procedure has been applied successfully by Montgomery to the synthesis of β-hydroxy-ester derivatives, see: (a) K. Subburaj, J. Montgomery. *J. Am. Chem. Soc.* **125**, 11210 (2003); (b) C. C. Chrovian, J. Montgomery. *Org. Lett.* **9**, 537 (2007).
11. All reactions presented in this study were monitored by gas chromatography.
12. (a) E. Le Gall, M. Troupel, J.-Y. Nédélec. *Tetrahedron Lett.* **47**, 2497 (2006); (b) E. Le Gall, M. Troupel, J.-Y. Nédélec. *Tetrahedron* **62**, 9953 (2006); (c) S. Sengmany, E. Le Gall, C. Le Jean, M. Troupel, J.-Y. Nédélec. *Tetrahedron* **63**, 3672 (2007); (d) C. Haurena, S. Sengmany, P. Huguen, E. Le Gall, T. Martens, M. Troupel. *Tetrahedron Lett.* **49**, 7121 (2008); (e) S. Sengmany, E. Le Gall, M. Troupel. *Synlett* 1031 (2008); (f) E. Le Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel. *J. Org. Chem.* **74**, 7970 (2009); (g) E. Le Gall, A. Decompte, T. Martens, M. Troupel. *Synthesis* 249 (2010); (h) C. Haurena, E. Le Gall, S. Sengmany, T. Martens, M. Troupel. *J. Org. Chem.* **75**, 2645 (2010).
13. (a) H. Fillon, C. Gosmini, J. Périchon. *J. Am. Chem. Soc.* **125**, 3867 (2003); (b) I. Kazmierski, C. Gosmini, J.-M. Paris, J. Périchon. *Tetrahedron Lett.* **44**, 6417 (2003); (c) C. Gosmini, M. Amatore, S. Claudel, J. Périchon. *Synlett* 2171 (2005).
14. THF solutions of organozinc reagents are commercially available (e.g., Aldrich).
15. (a) P. Knochel, P. Jones. In *Organozinc Reagents, A Practical Approach*, Oxford University Press, New York (1999); (b) J. E. Milne, S. L. Buchwald. *J. Am. Chem. Soc.* **126**, 13028 (2004).
16. M. Amatore, C. Gosmini, J. Périchon. *J. Org. Chem.* **71**, 6130 (2006).
17. S. Séka, O. Buriez, J.-Y. Nédélec, J. Périchon. *Chem.—Eur. J.* **8**, 2534 (2002).