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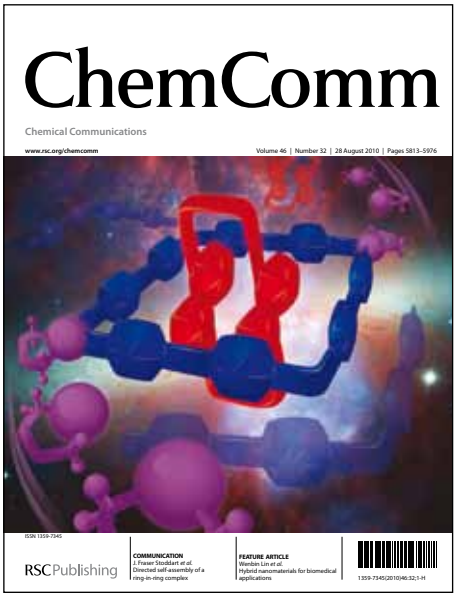

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ARTICLE TYPE

First One-pot organocatalytic synthesis of α-methylene-γ-lactones

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All in one pot: An Organocatalytic high enantioselective synthesis of α-methylene-γ-lactones has been reported. The reaction between protected 2-hydroxymalonates and MBH carbonates is simply catalysed by Chiral Lewis bases affording after acid treatment the corresponding lactones in excellent yields and enantioselectivities.

The α-Methylene-γ-lactone motif is a key structural element found in a vast number of biologically significant natural products, mainly of the Compositae family. The first α-methylene-γ-lactones were isolated over 100 years ago and were often used in traditional medicine for the treatment of inflammatory diseases. In recent years these compounds have been found to possess a broad spectrum of biological activities ranging from antimicrobial, antifungal, phytotoxic to cytotoxic/anti-cancer.[1] These diverse activities are associated with the presence of the highly electrophilic α-exo-methylene-γ-lactone moiety which can react via the Michael-type addition with nucleophilic sites on enzyme targets, resulting in the disruption of some major processes in the cell. For example α-methylene-γ-lactones can act as inhibitors of cellular steroids, blockers of tumour necrosis factor production, DNA polymerase inhibitors or apoptosis inducers.[2] Due to these inhibitory properties, α-methylene-γ-lactones have been tested as potential drug candidates.[3] α-Methylene-γ-lactone skeleton can be found in such natural products as arglabin, parthenolide, helenalin or (+)-paeonilactone (Figure 1).[4]

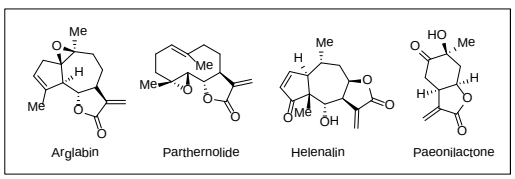


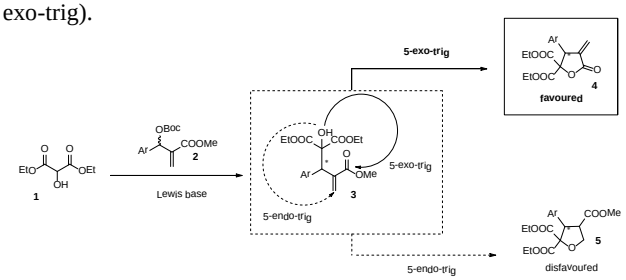
Figure 1: Structure of natural compounds with α-methylene-γ-lactone skeleton.

The main difficulty in the synthesis of compounds with α-methylene-γ-lactone motif is obtaining them in enantiopure form. The first example of enantioselective synthesis of α-exo-methylene-γ-lactones was reported recently by Krische and coworkers based on iridium-catalyzed C-C bond-forming transfer hydrogenation. In this work, alcohols react with acrylic ester affording the final lactones in excellent yields and enantioselectivities.[5]

In the literature, other organometallic asymmetric procedures for the synthesis of α-methylene lactones[6] can be found but they all rely on the use of chiral auxiliaries.

In the kingdom of organocatalysis, Jorgensen and coworkers reported an elegant asymmetric approach to α-methylene-δ-lactones and δ-lactams in 2008.[7] And only very recently, Liao and coworkers reported the non-asymmetric synthesis of α-methylene-γ-lactams via both a tandem allylic alkylation/amination protocol[8] and a multicomponent tandem organocatalytic reaction[9]

Remarkably, despite the interest in the synthesis of these compounds, a general enantioselective catalytic strategy for the synthesis of α-exo-methylene-γ-lactones remains an unmet challenge in organocatalysis. Here, we report the first enantioselective organocatalytic cascade[10] synthesis of α-methylene-γ-lactones by means of the asymmetric allyllic alkylation of Morita-Baylis-Hillman (MBH) carbonates with 2-hydroxy malonate. Based on our previous research in organocatalysis, [11] we envisioned an easy protocol for their synthesis via a nucleophilic addition of 1,3-dicarbonyl compounds to MBH carbonates (through a S_N2'-S_N2' mechanism) followed by an intramolecular lactonization (Scheme 1). Notably, the possible intramolecular Michael reaction between the hydroxyl with the conjugated double bond is disfavored (5-endo-trig) in comparison to the lactonization (5-exo-trig).

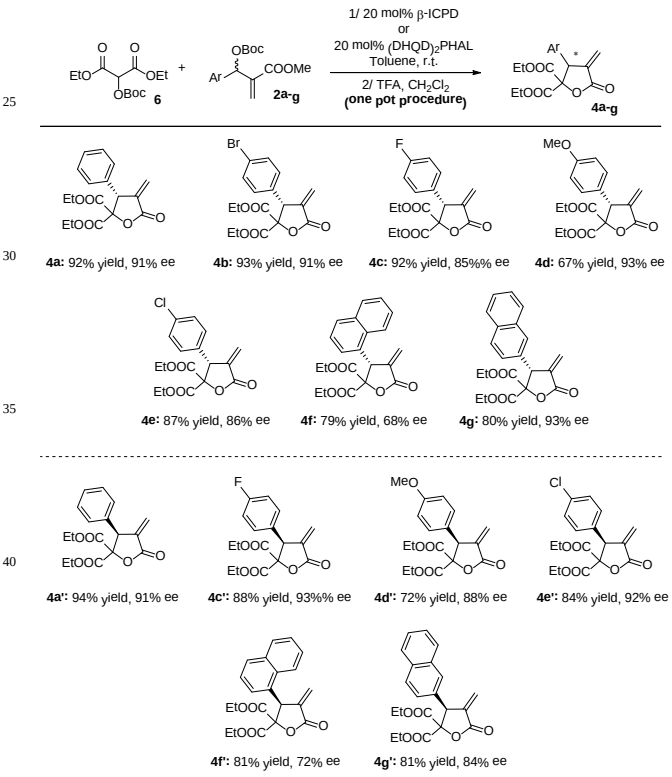


Scheme 1. Proposed reaction pathway

In the initial experiments, we used 2-hydroxy malonate **1** as a suitable nucleophile for the reaction. Unfortunately, only oxygen addition was observed in all the conditions tested. For this reason, we studied the use of Boc-protected hydroxyl malonate (**6**) in order to avoid O alkylation and obtain the C-addition product. In addition, Boc group could be easily "in situ" removed under acidic conditions that also will favour the later cyclization.

Satisfactorily, when Boc-protected 2-hydroxymalonate (**6**) and MBH carbonate **2** reacts in the presence of DABCO (20 mol%), the desired C-addition occurs. Moreover, the *in situ* deprotection of BOC under acidic conditions renders the α-methylene-γ-lactone **4**.

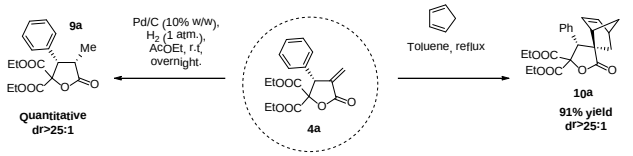
After optimization of the reaction conditions (see sup. Inf,) we found that toluene is the best solvent to carry out the reaction. In terms of catalysts the best results were obtained when β-isocupreine was used as catalyst, rendering the final α-methylene-γ-lactone 4a in 92% yield and 91% ee. Remarkably, when $(DHQD)_2PHAL$ was used as catalyst the reaction renders the final product 4a in 94% yield and 91% ee in longer reaction times enantioselectivities but with enantioselective induction opposite to that obtained with β-isocupreine. One of the most significant drawbacks in the use of cinchona-derived catalysts is the impossibility of deriving both enantiomers of the catalyst. However, we circumvented this drawback by using two different catalysts that render the products in excellent yields and excellent and opposite enantioselectivities, giving access to both the enantiomers of the product through a simple choice of the catalyst.



Scheme 2. Reaction Scope

With optimized conditions on hand, we proceeded to study the scope of the reaction. The reaction rendered the α-methylene-γ-lactones in excellent yields and in good enantioselectivities. For example, Ph, 4-BrC_6H_4, 4-$OMeC_6H_4$, or 4-FC_6H_4 or 2-Naphtyl MBH carbonates rendered the final α-methylene-γ-lactones in excellent yields and enantioselectivities when β-ICPD was used as catalyst (compounds **4a-d, 4g**: Scheme 2). 4-ClC_6H_4 generates the final lactone with slightly worse enantioselectivity. Notably, when bulky substituents such as 2-Naphtyl were used the enantiomeric excess (ee) of the reaction decreased by as much as 68% likely due a steric interaction between the MBH carbonate and the catalyst. As stated previously, the use of $(DHQD)_2PHAL$ gives access to the opposite enantiomers of the final products with excellent results. Compounds **4a′**, **4c′-e′** and **4g′** were obtained in good yields and excellent opposite enantioselectivities. Again, when bulky substituents, such 2-napthyl were used, the lactone **4f′** was obtained with only 72% ee.

The synthetic applicability of this methodology was exemplified by the transformation of **4a** in different products. For example, **4a** reacts with cyclopentadiene, rendering the Diels Alder adduct **10a** in satisfactory yields and total diastereoselectivity. Moreover, the hydrogenation of the exo-methylene double-bond of **4a** affords product **9a** in quantitative yields and a diastereopure form (*cis* conformation determined by NMR studies) (Scheme 3).



Scheme 3. Derivatization of **4a**

The absolute configuration for α-methylene-γ-lactones was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.[13] Four different methods (functionals) and two different basis sets were used to ascertain if different theoretical levels provided consistent shapes of the simulated spectra. Simulations were performed using BH&HLYP, M06-2X, LC-ωB97XD and CAM-B3LYP, together with the 6-311++G(2d,p) or the def2-TZVP basis sets. The spectra calculated assuming the *R* configuration match very well the experimental spectra of **4b** (using β-ICPD as catalyst.) The full conformational analysis and further details can be found in S.I.

Due to anticipated anti-cancer activity, lactones **4a-g** was tested against human leukemia HL-60 cell line. Cytotoxic activity of these compounds (IC_{50}) was expressed as the concentration (μM) required inhibiting tumor cell proliferation by 50% after 48 h exposure of the cells to a tested compound. Carboplatin was used as a reference compound. Obtained results are shown in Table 1. All tested compounds exhibited a consistent cytotoxic activity with IC_{50} values in the low micromolar range.

Table 1: Biological activity

Entry	Compound	Cytotoxicity IC_{50}^{*} (μM) HL-60
1	4a	0.94 + 0.08
2	4b	1.4 ± 0.15
3	4c	1.4 ± 0.23
4	4d	1.5 ± 0.17
5	4e	1.6 ± 0.13
6	4f	2.7 ± 0.31
7	4g	1.65 ± 0.21
8	Carboplatin	2.9 ± 0.05

* IC_{50} 50% inhibitory concentration represents the mean from dose-response curves of three independent experiments.

Conclusions

In summary, we developed a new enantioselective one-pot methodology for the synthesis of α-methylene-γ- lactones. Starting from MBH carbonates, the reaction renders α-methylene-γ-lactones in satisfactory yields and good enantioselectivities when commercially available chiral Lewis bases are used as catalysts. Moreover, we have easy access to both enantiomers of α-methylene-γ-lactones via the complimentary induction of β-ICPD and $(DHQD)_2PHAL$, making this methodology highly interesting for the synthesis of these compounds. Remarkably, this is the first report of the organocatalytic synthesis of α-exo-methylene-γ-lactones. Finally, the newly synthesized lactones were evaluated for their ability to inhibit the growth of human leukemia HL-60 cells, showing remarkable cytotoxicity. These results allow more compounds to be synthesized and evaluated, which could lead to the discovery of new drugs.

Acknoledgements

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General procedure for the synthesis of α-methylene-γ-lactones: In a vial equipped with a magnetic stirring bar, the corresponding MBH carbonate (0.2 mmol, 2 equiv.), O-Boc-hydroximalonate (0.1 mmol, 1 equiv.) and catalyst (0.02 mmol, 20 mol%) were added in 1.0 mL of toluene (C=0.1M), and the reaction was stirred at room temperature over a period of 1–5 days. After the consumption of the starting material (monitored by ^{1}H-NMR), the reaction crude was diluted with 1.0 mL of CH_2Cl_2;, 0.1 mL of TFA was added in one portion, and the mixture was stirred overnight. Then, 1.0 mL H_2O was added to the reaction crude; the mixture was neutralized with Na_2CO_3, and then extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$, and the organic solvent was eliminated at reduced pressure. The crude product that was purified by flash column chromatography to afford the desired α-methylene-γ-lactone.

Cytotoxicity assay: Human leucemia promyelocytic HL-60 cells were cultured in RPMI 1640 medium according with manufacturer's protocol. Cell viability was determined by the mitocondrial reduction assay (MTT) as described elswhere.[13]Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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