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First one-pot organocatalytic synthesis of α-methylene-γ-lactones†

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All in one pot: an organocatalytic highly 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] The α-methylene-γ-lactone skeleton can be found in natural products such as arglabin, parthenolide, helenalin or (+)-paeonilactone (Fig. 1).[4]

The main difficulty in the synthesis of compounds with the 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]

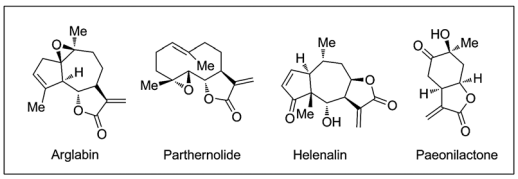

Fig. 1 Structure of natural compounds with α-methylene-γ-lactone skeleton.

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 co-workers reported an elegant asymmetric approach to α-methylene-δ-lactones and δ-lactams in 2008.[7] And only very recently, Liao and co-workers 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 an 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).‡

In the initial experiments, we used 2-hydroxy malonate **1** as a suitable nucleophile for the reaction. Unfortunately, only oxygen addition was observed under all the conditions tested.

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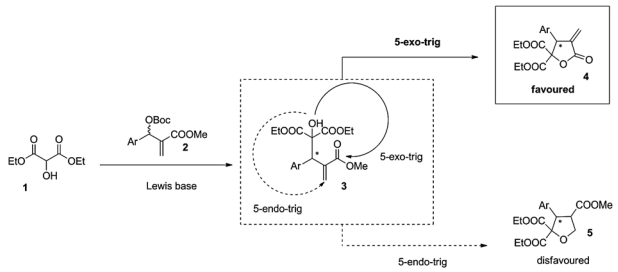


Scheme 1 Proposed reaction pathway.

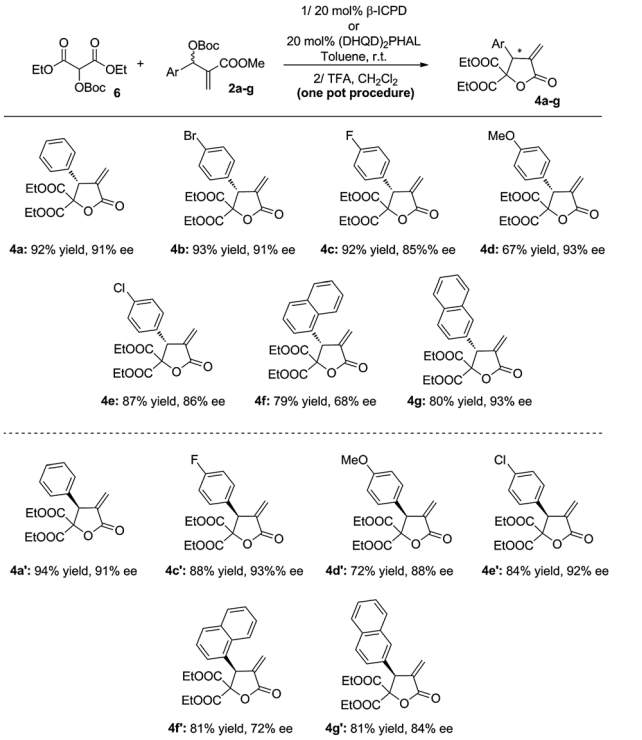
For this reason, we studied the use of Boc-protected hydroxyl malonate (**6**) in order to avoid *O*-alkylation and obtain the C-addition product. In addition, the Boc group could be easily removed "*in situ*" under acidic conditions, which will also favour the later cyclization.

Satisfactorily, when Boc-protected 2-hydroxymalonate (**6**) and MBH carbonate **2** react 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 ESI†) 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 a catalyst, rendering the final α-methylene-γ-lactone **4a** in 92% yield and 91% ee. Remarkably, when $(DHQD)_2PHAL$ was used as a catalyst the reaction renders the final product **4a** in 94% yield and 91% ee in longer reaction times 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 obtaining both enantiomers of the product. 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 catalyst.

With optimized conditions in 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-naphthyl MBH carbonates rendered the final α-methylene-γ-lactones in excellent yields and enantioselectivities when β-ICPD was used as a catalyst (compounds **4a–d** and **4g**: Scheme 2). 4-ClC_6H_4 generates the final lactone with slightly worse enantioselectivity. Notably, when bulky substituents such as 2-naphthyl were used the enantiomeric excess (ee) of the reaction decreased by as much as 68% likely due to 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 as 2-naphthyl were used, the lactone **4f′** was obtained with only 72% ee.

The synthetic applicability of this methodology was exemplified by the transformation of **4a** into different products. For example, **4a** reacts with cyclopentadiene, rendering the Diels–Alder adduct **10a** in satisfactory yields and total diastereoselectivity.[12] Moreover, the hydrogenation of the *exo*-methylene double-bond of **4a** affords



Scheme 2 Reaction scope.

Scheme 3 Derivatization of **4a**.

product **9a** in quantitative yields and in a diastereopure form (*cis* conformation determined by NMR studies) (Scheme 3).

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 ESI.†

Due to anticipated anti-cancer activity, lactones **4a–g** were tested against the human leukemia HL-60 cell line. Cytotoxic activity of these compounds (IC_{50}) was expressed as the concentration (μM) required for 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.§

In summary, we developed a new enantioselective one-pot methodology for the synthesis of α-methylene-γ-lactones.

Table 1 Biological activity

Entry	Compound	Cytotoxicity IC_{50}[a] (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

[a] IC_{50} 50% inhibitory concentration represents the mean from dose–response curves of three independent experiments.

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.

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Notes and references

‡ 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 a catalyst (0.02 mmol, 20 mol%) were added in 1.0 mL of toluene (C = 0.1 M), 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 of 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 was purified by flash column chromatography to afford the desired α-methylene-γ-lactone.

§ Cytotoxicity assay: human leukemia promyelocytic HL-60 cells were cultured in RPMI 1640 medium according to the manufacturer's protocol. Cell viability was determined by the mitochondrial reduction assay (MTT) as described elsewhere.[14]

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