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Enantioselective Organocatalytic Approach to δ-Lactones Bearing a Fused Cyclohexanone Scaffold

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ABSTRACT

A new method based on the cascade reaction between β,γ-unsaturated-α-ketophosphonates and cyclic 1,3-dicarbonyls is reported for the synthesis of highly enantiomerically enriched δ-lactones bearing a fused cyclohexenone scaffold. The target products bearing a δ-lactone moiety and one stereogenic center were obtained in good to excellent yields (83-96%) and enantioselectivities (63:32-95:5 er). The best results were obtained in the presence of a chiral Brønsted base catalyst derived from the cinchona alkaloid quinine and modified by a squaramide moiety.

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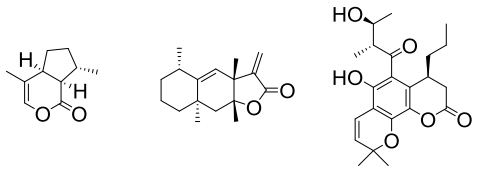
1. Introduction

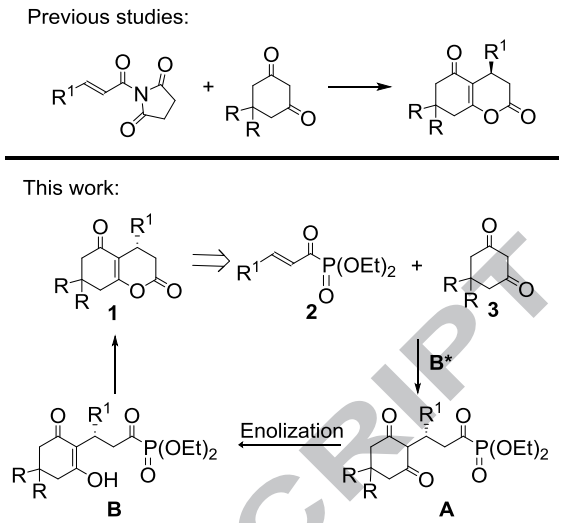
Chiral δ- and γ-lactone ring systems are common structural motifs in a variety of biologically interesting compounds and natural products.[1] In recent years, asymmetric organocatalysis has become an effective method of inducing chirality into target compounds, in which chiral organic molecules are used as promoters of selected chemical transformations.[2,3] Organocatalytic asymmetric cascade reactions are a powerful synthetic instrument leading to biologically important derivatives including δ- and γ-lactone core structures (Scheme 1).[3]



Scheme 1. Selected biologically active compounds containing γ- and δ-lactones structural motifs

For example, nepetalactone, isolated from the plant catnip (*Nepeta cataria*), shows sedative and analgesic effects in rats.[4] Alantolactone is present in elecampane (*Inula helenium*) and has potential activity against triple-negative breast cancer MDA-MB-231 cells by suppressing the signal transducer and activator of transcription 3 (STAT3) signaling pathway.[5] Finally, soulmarin exhibiting diverse biological activity was isolated from the stem bark of *Calophyllum soulattri*.[6]

Therefore, the main objective of this study was to develop a straightforward approach to bicyclic δ-lactones **1** bearing an additional cyclohexanone moiety. Recently, Zhao and Du demonstrated a facile route to this group of compounds based on the reaction between 1,3-dicarbonyl compounds and 1-cinnamoylpyrrolidine-2,5-dione derivatives (Scheme 2, top).[7] Given the importance of δ-lactones[1] and our interest in the application of acylphosphonates for the synthesis of biologically relevant molecules,[8,9] we postulated that acylphosphonates could serve as highly convenient precursors of this class of compounds (Scheme 2, bottom). The reaction mechanism involves: (i) organocatalytic Michael addition of pronucleophile **3** to electron-deficient olefin **2**; (ii) enolization; and (iii) lactonization to yield the target product **1**. In such a setup, the phosphonate moiety serves a triple purpose. Firstly, it activates the starting material making the double bond in **2** more electrophilic. Secondly, it enables efficient recognition of the catalyst through H-bonding interactions. Thirdly, the phosphonate moiety can be used as a good leaving group making the cyclization step (this occurs after the initial Michael addition and enolization) more feasible.

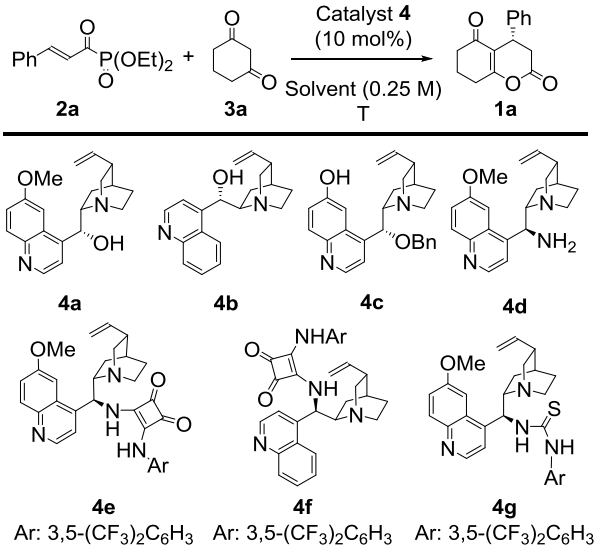


Scheme 2. Previous and present approaches to the target δ-lactones **1**

2. Results and Discussion

The optimization studies were performed using diethyl (*E*)-5-phenyl-3-benzylidenefuran-2(3*H*)-one **2a** and cyclohexane-1,3-dione **3a** as model reactants (Table 1). It was anticipated that the reaction should be possible using bifunctional catalysts bearing both Brønsted base and H-bond donor moieties (Scheme 2).[10] Initially, simple cinchona alkaloids such as quinine **4a** and cinchonine **4b** were employed as catalysts providing the desired δ-lactone **1a** efficiently, albeit with very low enantioselectivity (Table 1, entries 1-2). Therefore, modified alkaloids **4c-g** bearing more efficient H-bonding units were evaluated (Table 1, entries 3-7). In all cases, the reaction cascade proceeded efficiently; however, the stereochemical outcome of the reaction was strictly correlated to the H-bonding moiety present in the catalyst. Squaramide **4e**, derived from quinine, provided the highest enantioselectivity (Table 1, entry 5). The reaction was terminated within 24 hours and δ-lactone **1a** was obtained in 80% yield and 83:17 er. Various solvents were tested (Table 1, entries 8-11) and to our delight an enhancement of the reaction enantioselectivity (92:8 er) was observed in $CHCl_3$ (Table 1, entry 8). Finally, experiments were performed in order to evaluate the influence of reaction concentration (Table 1, entries 12-13) and temperature (Table 1, entries 14-17) on the enantioselectivity of the transformation. While, the reaction concentration had no beneficial impact on this parameter, an increase of the reaction temperature to 40 °C resulted in a further improvement of enantioselectivity, thus establishing optimal reaction conditions (Table 1, entry 15). At this stage the absolute stereochemistry of bicyclic δ-lactone **1a** was assigned as *R* by comparison of the sign of the specific rotation with that of enantiomerically pure material of known configuration.[7] The absolute configuration of products **1b-o** were assigned by analogy.

Table 1. Stereocontrolled synthesis of δ-lactones **1** – optimization studies[a]

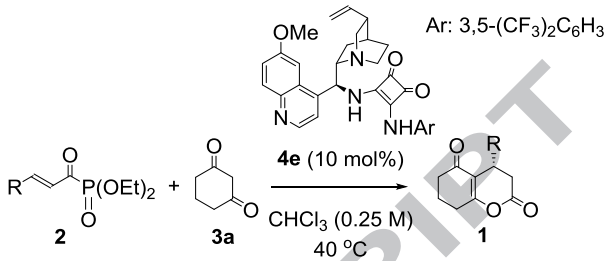


Entry	Solvent	Cat.	T [°C]	Yield [%][b]	er[c]
1	CH_2Cl_2	**4a**	RT	70	53:47
2	CH_2Cl_2	**4b**	RT	48	47:53
3	CH_2Cl_2	**4c**	RT	64	58:42
4	CH_2Cl_2	**4d**	RT	69	42:58
5	CH_2Cl_2	**4e**	RT	80	83:17
6	CH_2Cl_2	**4f**	RT	75	41:59
7	CH_2Cl_2	**4g**	RT	78	68:32
8	$CHCl_3$	**4e**	RT	89	92:8
9	$ClCH_2CH_2Cl$	**4e**	RT	80	83:17
10	Toluene	**4e**	RT	79	85:15
11	1,4-Dioxane	**4e**	RT	75	87:13
12[d]	$CHCl_3$	**4e**	RT	90	79:21
13[e]	$CHCl_3$	**4e**	RT	95	91:9
14	$CHCl_3$	**4e**	60	56	90:10
15	$CHCl_3$	**4e**	40	95	95:5
16	$CHCl_3$	**4e**	10	90	91:9
17	$CHCl_3$	**4e**	0	78	86:14

[a] Reactions performed on 0.1 mmol scale using **2a** (1 equiv.) and **3a** (1 equiv.) in 0.2 mL of the solvent (see ESI for detailed reaction conditions). [b] Isolated yield. [c] Determined by HPLC on a chiral phase. [d] Reaction performed in 0.4 mL of $CHCl_3$. [e] Reaction performed in 0.1 mL of $CHCl_3$.

With the screening studies accomplished, the substrate scope was explored (Table 2, Scheme 3). Initially, various diethyl (*E*)-β,γ-unsaturated-α-ketophosphonates **2** were reacted with cyclohexane-1,3-dione **3a** (Table 2). Various aromatic substituents in the γ-position of **2** were well-tolerated providing target δ-lactones **1a–l** in high yield (83-95%) and with good to high enantioselectivities (70:30-95:5 er) (Table 3, entries 1-12). Notably, the electronic properties of the substituent on the aromatic ring in **2** (Table 3, entries 1-6 *vs.* 7-9) had no significant influence on the reaction efficiency. Similarly, the reaction proved unbiased towards the position of the substituent on the aromatic ring in **2** (Table 3, entries 4-6 *vs.* 8-9). However, when chlorine was present in the *ortho* position a reduction in enantioselectivity was observed (Table 3, entry 6). Interestingly, disubstituted aromatic rings (Table 3, entries 10-11) and heteroaromatic substituents (Table 3, entry 12) could be present as demonstrated in the synthesis of **1j,k** and **1l**. Notably, the introduction of an alkyl chain in the γ-position of **2** was also possible providing products **1m**,**n** in high yields and with good enantioselectivity (Table 3, entries 13-14).

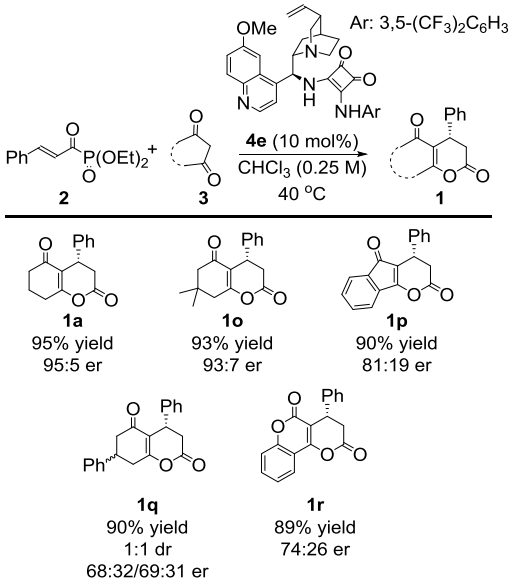
Table 2. Organocatalytic stereocontrolled synthesis of bicyclic δ-lactones **1** – (*E*)-β,γ-unsaturated-α-ketophosphonate **2** scope[a]



Entry	R	**1**	Yield [%][b]	er[c]
1	Ph	**1a**	95	95:5
2	4-$CF_3C_6H_4$	**1b**	90	90:10
3	4-BrC_6H_4	**1c**	94	92:8
4	4-ClC_6H_4	**1d**	96	84:16
5	3-ClC_6H_4	**1e**	84	89:11
6	2-ClC_6H_4	**1f**	83	70:30
7	4-MeC_6H_4	**1g**	92	88:12
8	4-$MeOC_6H_4$	**1h**	93	89:11
9	2-$MeOC_6H_4$	**1i**	94	85:15
10	1-naphthyl	**1j**	91	86:14
11	3,4-$OCH_2OC_6H_3$	**1k**	90	90:10
12	2-furyl	**1l**	94	85:15
13	CH_3	**1m**	91	86:14
14	C_6H_{13}	**1n**	92	88:12

[a] Reactions performed on 0.1 mmol scale (see ESI for detailed reaction conditions). [b] Isolated yield. [c] Determined by HPLC on a chiral phase.

In the course of further studies, various 1,3-dicarbonyl compounds **3** were evaluated (Scheme 3). Various cyclic 1,3-diketones such as dimedone **3b**, 1,3-indanodione **3c** and 5-phenylcyclohexane-1,3-dione **3d** were successfully employed in the reaction cascade. Notably, δ-lactone **1q** which possesses an additional stereogenic center was obtained as a mixture of two diastereoisomers in a 1:1 ratio. To our delight, the reaction cascade also proceeded efficiently using 4-hydroxycoumarin **3e**. Notably, in this case the formation of cyclic product **1r** was observed.[11]



Scheme 3. Organocatalytic stereocontrolled approach to bicyclic δ-lactones **1** – 1,3-diketone **3** scope

3. Summary

In conclusion, we have developed a new organocatalytic approach to δ-lactones bearing a fused cyclohexanone scaffold. The reaction cascade relies on the application of β,γ-unsaturated-α-ketophosphonates **2** as key intermediates. It was demonstrated that the application of a bifunctional organocatalyst derived from cinchona alkaloids that bears both a Brønsted base moiety and H-bond donor enables the efficient recognition of both substrates. As a consequence the reaction proceeded efficiently with moderate to high levels of stereocontrol. Notably, our approach is complementary to Zhao and Du's strategy[11] with the main benefits relating to the usage of β,γ-unsaturated-α-ketophosphonates **2** as highly convenient and effective α,β-unsaturated acid surrogates.[8b]

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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Graphical Abstract

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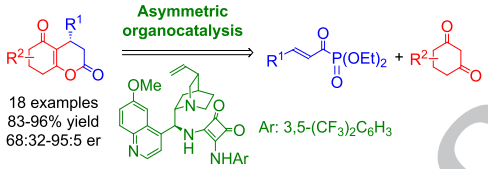

- Stereoselective approach to bicyclic δ-lactones bearing a fused cyclohexanone scaffold.
- Bioinspired targets.
- Convenient starting materials.