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Asymmetric synthesis of new γ-butenolides via organocatalyzed epoxidation of chalcones†

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Abstract: γ-Butenolides have been recognized as an important structural framework in a number of natural products and medicinally important agents. In this work we describe a new metal-free sequential strategy for the asymmetric synthesis of substituted γ-butenolides having epoxychalcones as advanced intermediate. Using the optimized reaction conditions, we were able to carry out the three-step sequence, epoxidation, olefination and hydrolysis, with only one single chromatographic purification of the final product, furnishing new enantiomerically enriched γ-butenolides in moderate overall yield and good enantiomeric excess.

Keywords: epoxychalcones, organocatalysis, olefination, microwaves, green synthesis

γ-Butenolides have been recognized as an important structural framework in a number of natural products and medicinally important agents, e.g. ascorbic acid, (-)-iso-cladospolide B, isolated from *Cladosporium* sp,[1] and saxorumamide, an alkaloid obtained from *Stemona saxorum*.[2] Miao and Andersen reported the isolation of metabolites of the colonial tunicate *Ritterella rubra*, named rubrolides A-H which showed antibacterial activity.[3] More recently, Kang *et al*. have synthesized rubrolide analogues with antibiotic and immunosuppressant properties (Figure 1).[4]

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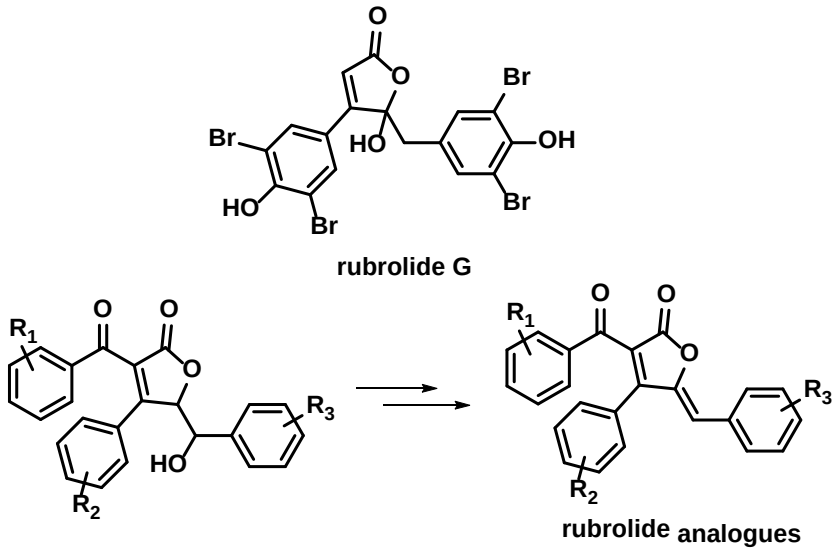

Figure 1 Examples of biologically active γ-butenolides.

Due to their biological importance, several strategies towards the synthesis of γ-butenolides has been explored.[5] In this regard, the catalytic asymmetric vinylogous-type reactions of γ-butenolides have received growing attention, because the resulting enantiomerically pure γ-substituted butenolides are versatile building blocks for various natural products and biologically active compounds. Among which, the vinylogous aldol reaction,[6] vinylogous Mannich reaction,[7] vinylogous Michael reactions,[8] as well as allylic alkylation reaction have been well developed in the past two decades, by using either chiral Lewis acid catalysis or organocatalysts. Among the plethora of catalytic systems developed so far, vinylogous Mukaiyama-type reactions using 2-silyloxyfurans as the nucleophiles are popular for the synthesis of γ-substituted butenolides.[9]

Devalankar *et al*. reported a sequential strategy that involves an organocatalytic α-aminoxylation followed by Wittig olefination to afford γ-butenolides as the major product in good yields and excellent enantiomeric excess.[10] A gold(I)-catalyzed cascade cyclization−oxidative cross-coupling process has been applied to prepare β-alkynyl-γ-butenolides directly from allenoates and various terminal alkynes.[11]

Furthermore, Patil *et al*. described a catalytic cross-coupling reaction of tert-butyl allenoates with diazonium salts under a cooperative catalysis (photoredox and gold (I)) in which the corresponding butenolides were delivered in good to excellent yields (Scheme 1a).[12] Dénès and co-authors reported the

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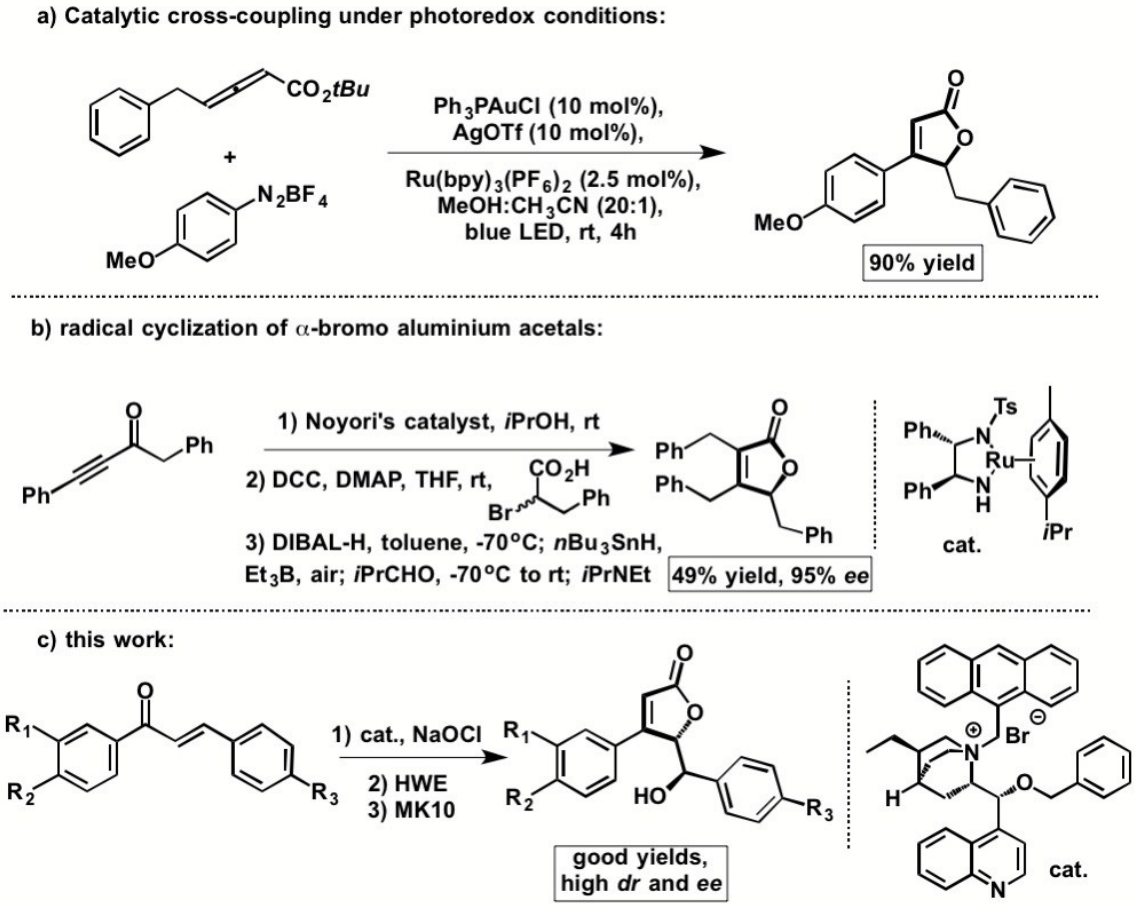
synthesis of polysubstituted butenolides from α-bromoesters derived from propargyl alcohols by a one-pot reaction involving the radical cyclization of α-bromo-aluminium acetals, followed by the oxidation of the resulting cyclic aluminium acetals in an Oppenauer-type process and migration of the exocyclic C=C bond into the α,β-position. Using this procedure, the total synthesis of maculalactone A was accomplished (Scheme 1b). The configuration of the chiral centre was set using asymmetric reduction of ynone using Noyori's ruthenium-based catalyst.[13]



Scheme 1 Synthesis of γ-butenolides.

We describe in this work a new metal-free sequential strategy for the asymmetric synthesis of substituted γ-butenolides having epoxychalcones as intermediate (Scheme 1c). Optically active epoxyketones are versatile building blocks for the synthesis of several natural products and pharmaceuticals.[14] In this context, the development of efficient methods for the asymmetric epoxidation of α,β-enones is an interesting goal in organic synthesis. Therefore,

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a number of organocatalyzed[15] and metal-catalyzed[16] protocols have been developed for the epoxidation of electron-deficient olefins in a stereoselective manner.

In this way, independently, Lygo and Corey have shown that *N*-anthracenylmethyl-substituted ammonium salts with the C-9 hydroxyl groups being protected as benzyl ethers are effective catalysts for epoxidation of α,β-unsaturated ketones using NaOCl or KOCl as oxidant.[17,18] Motivated by these previous results, new types of bis-quaternary ammonium bromide as chiral multisite phase transfer catalysts have been developed and evaluated for the enantioselective epoxidation of chalcones in the presence of lower concentrations of various oxidants, bases and ultrasonic irradiation conditions.[19]

In order to obtain the epoxychalcones, different catalysts and oxidants were first evaluated in the epoxidation reaction (Table 1). The organocatalysts **1**-**6** were synthesized as previously described (Figure 2).[20]

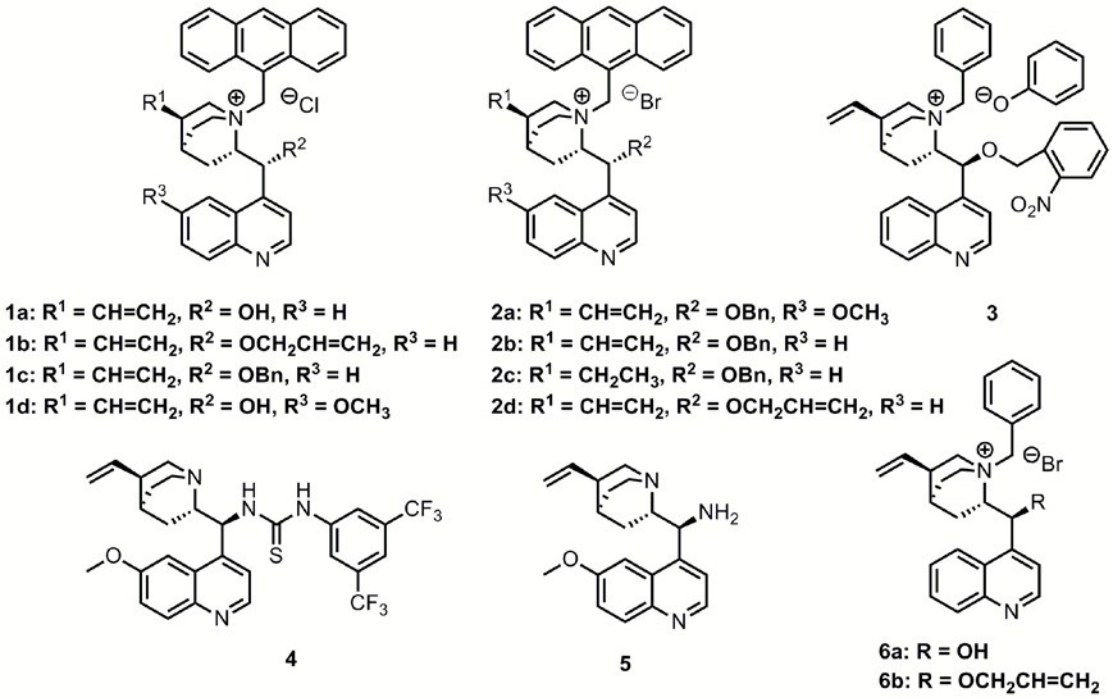

Figure 2 Organocatalysts evaluated on the epoxidation of chalcone.

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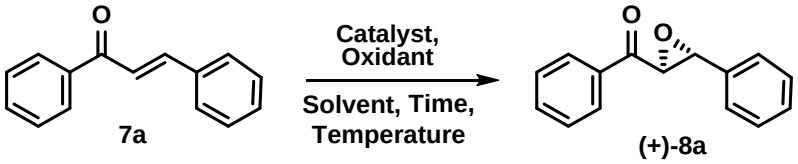
Table 1 Optimization of the epoxidation reaction of chalcone **7a**.



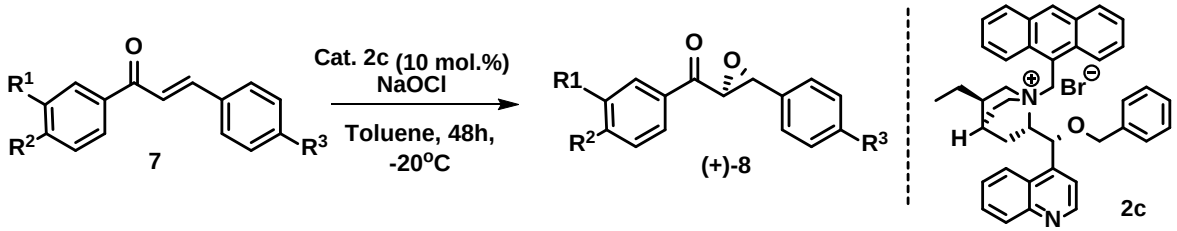
Entry	Catalyst	Oxidant	Solvent	Additive	Time (h)	T (°C)	Yield (%)[h]	*ee* (%)[i]
1	**1a**	NaOCl	Toluene	-	48	rt	78	44
2	**1b**	NaOCl	Toluene	-	48	rt	7	75
3	**1c**	NaOCl	Toluene	-	48	rt	3	nd[k]
4	**1d**	NaOCl	Toluene	-	48	rt	63	46
5	**2a**	NaOCl	Toluene	-	48	rt	64	64
6	**2b**	NaOCl	Toluene	-	48	rt	67	34
7	**2c**	**NaOCl**	**Toluene**	**-**	**48**	**-20**	**64**	**85**
8	**2c**	NaOCl	Ph_2O	-	12	rt	86	80
9	**2c**	NaOCl	DCM	-	12	rt	66	60
10	**2c**	NaOCl	Hexane	-	12	rt	34	25
11	**2c**	NaOCl	THF	-	12	rt	-[j]	-
12	**2c**	NaOCl	Xylene	-	12	rt	81	80
13	**2c**	NaOCl	Tol:DCM	-	12	rt	95	80
14	**2d**	NaOCl	Toluene	-	48	rt	63	66
15	**3**	NaOCl	Toluene	-	48	rt	60	26
16[c]	**4**	H_2O_2	THF	-	24	rt	-[j]	-
17[c]	**4**	H_2O_2	Dioxane	-	24	50	4	0
18[c]	**5**[a]	H_2O_2	Dioxane	TFA[b]	72	rt	-[j]	-
19[c]	**5**[a]	H_2O_2	Dioxane	TFA[b]	24	50	5	80
20[d]	**5**[a]	*t*-BuO_2H	Dioxane	TFA	48	50	14	72
21[d]	**5**[a]	*m*-CPBA	Dioxane	TFA	48	50	8	10
22[e]	**5**[a]	H_2O_2	Toluene	TFA	48	60	-[j]	-
23[e]	**5**[a]	H_2O_2	Hexane	TFA	48	60	-[j]	-
24[f]	**5**[a]	H_2O_2	EtOH	TFA	48	50	-[j]	-
25[f]	**5**[a]	H_2O_2	MeOH	TFA	48	50	-[j]	-
26[g]	**5**[a]	H_2O_2	Dioxane	CH_3SO_3H	48	50	-[j]	-
27[g]	**5**[a]	H_2O_2	Dioxane	*p*-$NO_2C_6H_4CO_2H$	48	50	6	74
28[g]	**5**[a]	H_2O_2	Dioxane	$C_6H_5CO_2H$	48	50	6	70

29[g]	**5**[a]	H_2O_2	Dioxane	*o*-$NO_2C_6H_4CO_2H$	48	50	6	82
30	**6a**	NaOCl	Toluene	-	48	rt	11	0
31	**6b**	NaOCl	Toluene	-	48	rt	8	0

Unless otherwise noted, all reactions were carried out with chalcone **7a** (0.144 mmol) using 1 mL of solvent, 2 equiv. of oxidant, 10 mol% of catalyst and 40 mol% of additive. [a] 20 mol% of catalyst. [b] 20 mol% of additive. [c] 0.245 mmol of **7a**. [d] 0.315 mmol of **7a**. [e] 0.289 mmol of **7a**. [f] 0.37 mmol of **7a**. [g] 0.176 mmol of **7a**. [h] Isolated yields after column chromatography. [i] Measured by HPLC with chiral column. [j] Starting material recovered. [k] nd = not determined.

Using the optimized conditions (entry 7), the epoxychalcones **8** were obtained from chalcones **7** employing the *N*-anthracenylmethyl-substituted ammonium salt **2c** as described by Corey *et al*. (Table 2).[18] The stereochemical course of the epoxidation reaction employing catalyst **2c** provided the desired products **8a**-**f** in a good yields and high enantiomeric excess.

Table 2 Asymmetric epoxidation using phase-transfer organocatalyst **2c**.



Epoxychalcone	R^1	R^2	R^3	Yield (%)[a]	*ee* (%)[b]
8a	H	H	H	64	85
8b	H	H	Cl	83	87
8c	O-CH_2-O		Br	68	96
8d	H	Br	H	68	81
8e	H	OCH_3	H	72	91
8f	H	H	NO_2	90	92

Unless otherwise noted, all reactions were carried out with chalcone **7** (0.144 mmol) using 1 mL of solvent, 2 equiv. of oxidant, 10 mol% of catalyst. [a]Isolated yields after column chromatography. [b] Measured by HPLC with chiral column.

We then turned our attention to the γ-butenolides synthesis. In this regard, the epoxyester (±)-**9a** was synthesized as described by Tarver *et al.*

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starting from the corresponding epoxychalcone.[21] The racemic epoxychalcone **8a** was obtained employing H_2O_2 as oxidant and NaOH in MeOH[22] and then submitted to the Horner–Wadsworth–Emmons (HWE) reaction, with triethyl phosphonoacetate and sodium hydride in dry THF under reflux for 3h.[21] Under these standard conditions, the corresponding racemic epoxyester **9a** was obtained in 71% yield. Finally, the hydrolysis of epoxyester **9a** followed by intramolecular esterification was investigated with different catalysts[23] as well as conventional and biobased solvents[24] (Table 3).

The best result and using a greener condition was achieved with 15% w/w of montmorillonite K10 (MK-10) clay, ethanol as solvent, for 7 hours at room temperature in which delivered the desired γ-butenolide **10a** in 96% isolated yield (entry 16). The selective formation of **10a** instead of the δ-pentenolide **11** was confirmed by NMR experiments. The HMBC spectrum showed a $^4J_{C\text{-}H}$ correlation between the C5 (δ 84.0) with the hydrogen at *ortho* position of B ring and, in the NOESY, H5 correlates with both H6 and the OH suggesting free rotation of the C5-C6 bond (Figure 3).

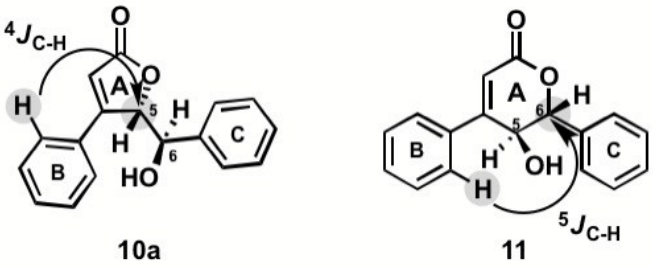

Figure 3 γ-Butenolide **10a** *vs* δ-pentenolide **11**.

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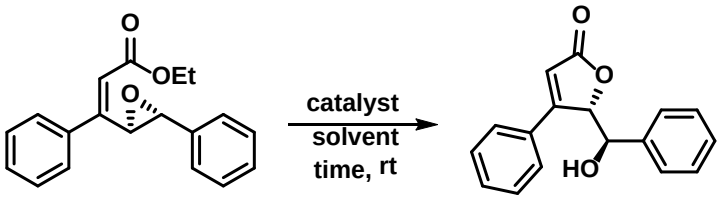
Table 3 Optimization studies for hydrolysis and cyclization.



(±)-9a (±)-10a

Entry	Catalyst	Solvent	Time (h)	Yield (%)[k]
1	PTSA[a]	MeOH	14	50[i]
2	TFA[a]	MeOH	14	55
3	Amberlyst 15[b]	MeOH	14	58
4	Benzoic acid[a]	MeOH	14	42
5	MK 10[a]	MeOH	14	84
6	$AlCl_3$[a]	MeOH	14	41
7	$BF_3.Et_2O$[a]	MeOH	14	---[j]
8	TFA[a]	EtOH	0.5[h]	68
9	Amberlyst 15[g]	EtOH	0.5[h]	67
10	Benzoic acid[a]	EtOH	0.5[h]	83
11	$AlCl_3$[a]	EtOH	0.5[h]	74
12	MK 10[c]	EtOH	14	90
13	MK 10[d]	EtOH	14	91
14	MK 10[f]	EtOH	14	81
15	MK 10[e]	EtOH	14	86
16	**MK 10[d]**	**EtOH**	**7**	**96**
17	MK 10[c]	DCM	14	58
18	MK 10[c]	Toluene	14	78
19	MK 10[a]	THF	14	75
20	MK 10[a]	Et_2O	14	72
21	MK 10[c]	PEG 400	14	34
22	----	EtOH	14	11

Unless otherwise noted, all reactions were carried out with 0.170 mmol (1 equiv) of **9a** and 1 mL of solvent. [a] 0.25 equivalent. [b] 30% weight. [c] 25% weight. [d] 15% weight. [e] 10% weight. [f] 5% weight. [g] 13% weight. [h] microwave irradiation at 100 °C and 300 W, 0.150 mmol of **9a** and 1 mL of solvent. [i] 0.340 mmol of **9a** and 2 mL of solvent. [j] Complex mixture. [k] After chromatographic purification.

We then evaluated the olefination and hydrolysis reactions in a one-pot fashion, only changing the solvent between the two steps. To our delight, the desired γ-butenolide (±)-**10a** was obtained from epoxyketone (±)-**8a** in 68% yield

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over two steps (Scheme 2). The scope and limitations of this method was further explored with electron withdrawing and donating groups on both A and B rings of the chalcone, affording γ-butenolides (±)-**10b-j** in good overall yields. It is worth to note that no steric hindrance effects were observed since this method could be applied to chalcone (±)-**7g** containing a methoxy group at the *orto* position of the A ring, leading to (±)-**10g** in good overall yield.

Furthermore, chalcones possessing heterocyclic aromatic rings were also evaluated and successfully afforded the corresponding furan and thiophen derivatives (±)-**10k** and (±)-**10l**, respectively. However, *N*-heterocyclic chalcones did not furnished the desired products. For example, the epoxidation of 3-(1H-indol-2-yl)-1-phenyl-2-propen-1-one[25] failed whereas for the pyridine derivative,[26] no formation of the desired product (±)-**10m** was observed, with recovery of either the corresponding unreacted epoxyketone (±)-**7m** or the Wittig adduct (±)-**9m** from the olefination step.

Aiming to provide a greener reaction condition for this novel protocol, we performed additional experiments using microwave irradiation.[27] After short optimization, the olefination reaction of epoxyketone (±)-**8a** was carried out at 90ºC (300 W) for 30 min then the solvent (THF) was evaporated and EtOH and MK-10 were added. This mixture was again submitted to microwave irradiation at 100ºC (300 W) for 30 min furnishing the γ-butenolide (±)-**10a** in 66% yield (Table 4, entry 1). In order to demonstrate the applicability of this reaction, this procedure was also successfully applied to epoxyketones (±)-**8b-d** leading to the corresponding γ-butenolides (±)-**10b-d** (Table 4, entries 2-4) and in all cases the reaction yields under microwave irradiation were similar or even higher than the conventional procedure.

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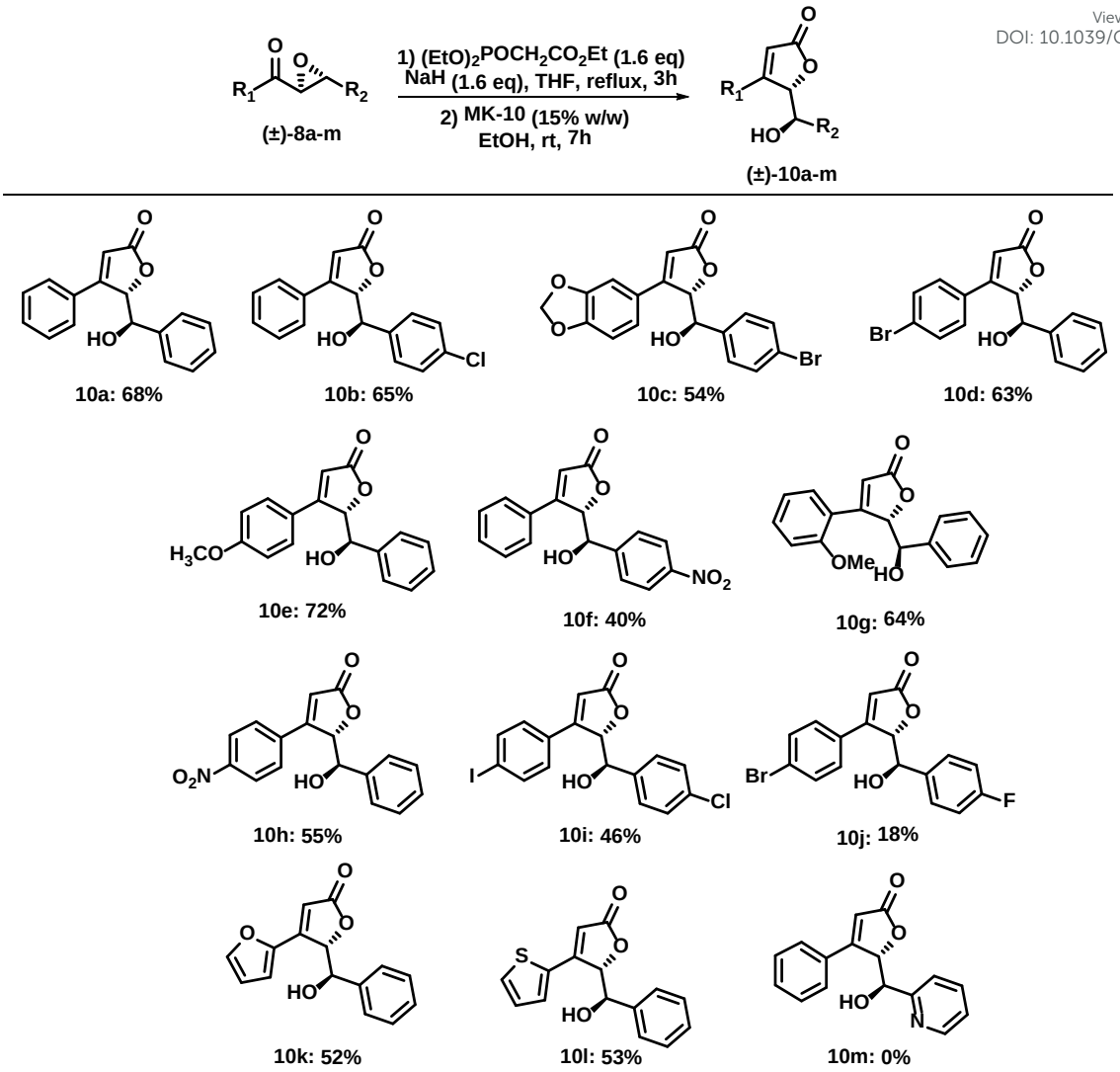
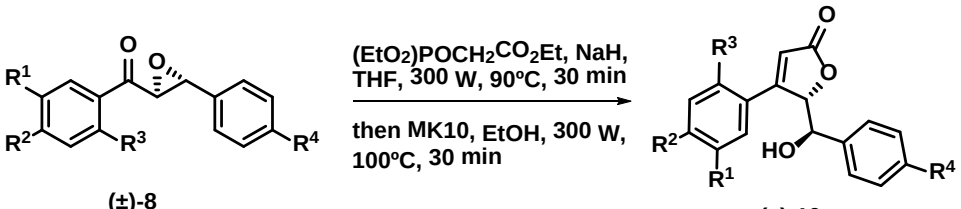


Scheme 2 Scope and limitation on the synthesis of *γ*-butenolides.

Table 4 Synthesis of γ-butenolides under microwave irradiation.



Compound	R_1	R_2	R_3	Yield (%)[a]
10a	H	H	H	66
10b	H	H	Cl	64
10c	O-CH_2-O		Br	67
10d	H	Br	H	80

[a] Overall yield after chromatographic purification.

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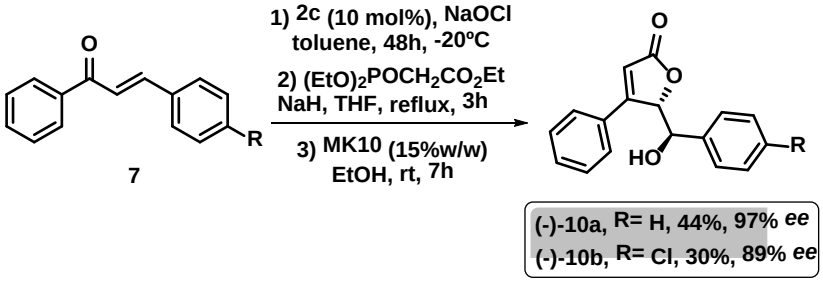
Moreover, we were also able to carry out the three-step sequence, in its asymmetric version to this end, the epoxidation, olefination and hydrolysis required only a single chromatographic purification of the final product. Thus, employing the optimized conditions described above, the enantiomerically enriched γ-butenolides (-)-**10a** and (-)-**10b** were obtained in moderate overall yield and good enantiomeric excess (Scheme 3).



Scheme 3 Asymmetric synthesis of γ-butenolides (-)-**10a** and (-)-**10b**.

In conclusion, we have developed a new methodology for the synthesis of γ-butenolides from chalcones in a short reaction sequence. Furthermore, the epoxychalcones were converted to γ-butenolides in greener conditions, reducing several chromatographic purifications,[28] minimizing the waste chemicals generation and saving time.

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A greener three-step sequence, with only one single chromatographic purification, afforded γ-butenolides in moderate overall yield and high enantiomeric excess.