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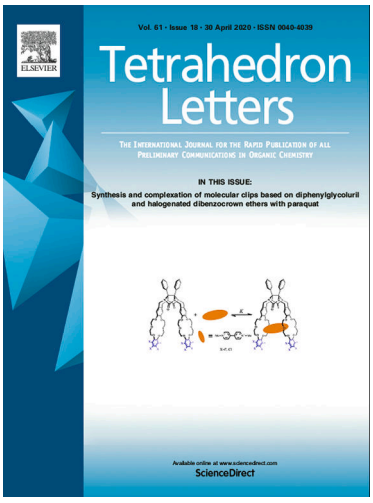

Oxiranyl remote anions from epoxy cinnamates and their application towards the synthesis of α,β-epoxy-γ-butyrolactones

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Oxiranyl remote anions from epoxy cinnamates and their application towards the synthesis of α,β-epoxy-γ-butyrolactones

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ABSTRACT

A series of α,β-epoxy-γ-butyrolactones were synthesized in moderate yields *via* oxiranyl remote anions derived from epoxy cinnamate esters. The key synthetic step involved deprotonation of the β-position of α,β-epoxy cinnamate derivatives where the generated β-anion was stabilized by remote chelation from an ester group. The substitution reaction of the anion with a variety of ketones, followed by cyclization, readily furnished the desired substituted α,β-epoxy-γ-butyrolactones.

Due to its characteristic ring strain and polarized C-O bond, epoxides are able to react with a large number of reagents including nucleophiles, electrophiles, acids, and bases.[1] The reaction of an epoxide with a strong base typically generates an oxiranyl anion which can further react with a variety of electrophiles to provide polysubstituted epoxides. In certain cases, deprotonation by a lithium base could occur at the β-position of an epoxide and the stability of the anion could be enhanced by a chelating group, *e.g.* ester, oxazoline, ketone, lactone, ether, or pyridine moieties (Fig.1).[2-8]

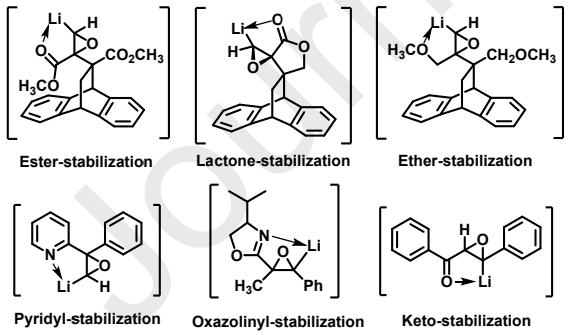
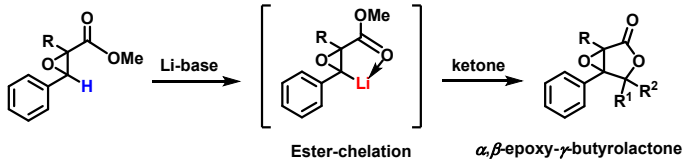


Figure 1. Representative stabilizing groups for the oxiranyl "remote" anion.

Substituted epoxides exhibit numerous biological activities such as anticancer,[9,10] anti-inflammatory,[11] antifungal,[12] and antibiotic agents.[13] Among them, α,β-epoxy-γ-butyrolactones which combine two versatile functional skeleta, *i.e.* epoxide and butyrolactone, have been observed in naturally occurring compounds[14] or their intermediates.[15-16]

The synthesis of α,β-epoxy-γ-butyrolactones from epoxide intermediates have been investigated.[14] In 2017, Leiyang and co-workers reported the synthesis and structural revision of an antifungal agent, (±)-clavilactone D, *via* selective cyclization of an α,β-dicarbonyl peroxide using the three-component reaction of benzaldehyde, an alkene, and TBHP.[14] Thus, to extend the scope of the chemistry of an oxiranyl remote anion, in this work we wish to report the application of oxiranyl remote anions as an alternative approach for the synthesis of α,β-epoxy-γ-butyrolactones (Scheme 1).



Scheme 1. Synthesis of α,β-epoxy-γ-butyrolactones *via* oxiranyl remote anions.

Our work started with the preparation of epoxy cinnamates **5** and **6** *via* the epoxidation of the methyl ester derived from α-methyl cinnamic acid **1** and α-phenyl cinnamic acid **2**, respectively (Scheme 2). Next, the epoxy cinnamates **5** and **6** were treated with lithium diisopropylamide (LDA) in the presence of various electrophiles to generate a series of β-substituted epoxides.

The model reaction of epoxide **5** and ethyl chloroformate was used to optimize the reaction conditions, see Table 1. Treatment of the mixture of epoxide **5** and 3 equivalents of ethyl chloroformate in THF with 3 equivalents of lithium diisopropylamide (LDA) at –78 °C generated an anion *in situ*, which was followed by reaction with an electrophile to furnish the substituted product **7c** in an optimal 42% yield (Entry 3).

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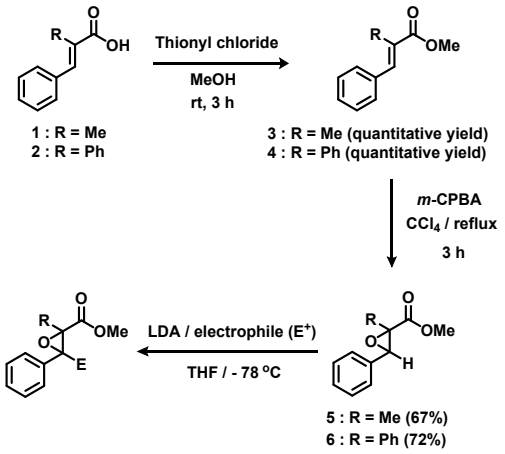
E-mail address: tienthong.tho@mahidol.ac.th (T. Thongpanchang).

Dec ...as desired product (Entry 1).

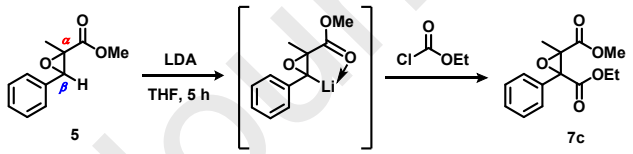
The use of three equivalents of LDA was optimal since an increase to 5 equivalents (Entry 5) did not increase the yield. Increasing the amount of the electrophile to more than 3 equivalents did not benefit the reaction (Entry 4). Moreover, the temperature played a key role in this reaction, *i.e.* the reaction at 0 °C or at room temperature gave only trace amounts of the product. In addition, the sequence of reagent addition was also investigated. When epoxide **5** was treated with LDA followed by the addition of ethyl chloroformate, both product **7c** (41%) and the self-condensation product **9** (18%) were obtained (Entry 8). Since the sequence of the reagent addition did not affect the yield of product **9**, the protocol where all starting materials were mixed prior to the addition of a lithium base was preferred.



Scheme 2. Synthesis of *α,β*-epoxy cinnamate methyl esters and the reaction of their corresponding remote anions.

Subsequently, the reactions of the remote anion generated from epoxy cinnamate derivatives **5** and **6** were investigated with trimethylsilyl chloride, tributyltin chloride, ethyl chloroformate, and phenyl chloroformate as electrophiles to extend the scope of the reaction. The corresponding products were obtained in moderate yields as shown in Table 2.

Table 1. Optimization of the reaction conditions for the *β*-deprotonation of epoxy ester **5**.

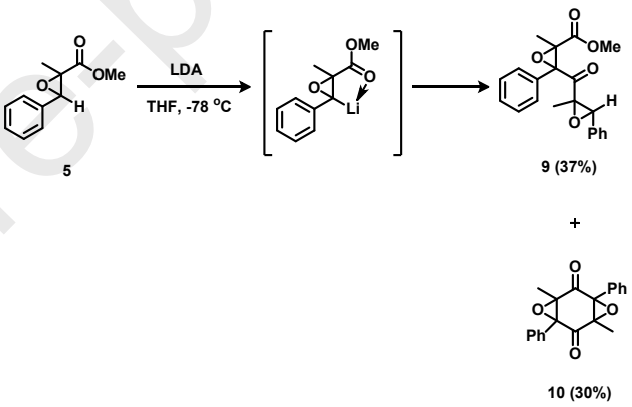


Entry	LDA (eq.)	Ethyl chloroformate (eq.)	Temperature (°C)	Yield 7c (%)
1	1	1	-78	Not observed
2	3	2	-78	22
3	3	3	-78	42
4	3	5	-78	31
5	5	5	-78	26
6	3	3	0	Trace
7	3	3	rt	Trace
*8	3	3	-78	41

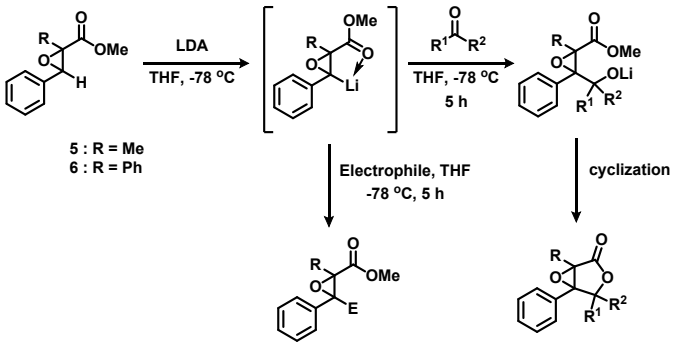
* In the case of the sequential method, the desired product **7c** was observed along with methyl 2-methyl-3-(2-methyl)-3-phenyloxirane-2-(carbonyl)-3-phenyloxirane-2-carboxylate **9**

confirmed by selective NOE experiments.[17] For example, in the case of compound **8a**, the methyl ester proton at 3.82 ppm was enhanced upon irradiation at the trimethylsilyl proton at 0.10 ppm (H). This result evidently identified that *β*-deprotonation and reaction with TMSCl proceeded *syn* to the ester group.

In a separate experiment, the reaction of epoxide **5** with LDA in the absence of an external electrophile gave methyl 2-methyl-3-(2-methyl-3-phenyloxirane-2-carbonyl)-3-phenyl-oxirane-2-carboxylate (**9**) and 3,6-dimethyl-1,4-diphenyl-7,8-dioxatricyclo[2.1.1] octane-2,5-dione (**10**) in 37% and 30% yield, respectively (Scheme 3). The formation of product **10** could be rationalized by the subsequent *β*-deprotonation of dimer **9** followed by intramolecular substitution of the new remote anion with the ester group. This finding could lead to an alternative pathway for the synthesis of other epoxide derivatives containing a benzoquinone backbone. The formation of cyclization product **10** also suggested the possibility to apply this remote anion strategy to the synthesis of *α,β*-epoxy-*γ*-butyrolactones. Thus the reaction of epoxides **5** and **6** with LDA generated oxiranyl anions which could further add to a carbonyl electrophile to form an alkoxide intermediate. Subsequent intramolecular cyclization then furnished the desired butyrolactones as shown in Scheme 4. The reaction was compatible with a variety of ketones as electrophiles and the product yields are summarized in Table 3.



Scheme 3. Oxiranyl remote anion reaction without an electrophile.



Scheme 4. Reaction of oxiranyl remote anions from *α,β*-epoxy carbonyl compounds.

When asymmetric ketones were used as the electrophile, a pair of diastereomeric products, *e.g.* compound **7g**, could be expected. Unexpectedly, in the case of **7f**, **8f**, and **8g**, only a single diastereomer was isolated by preparative TLC purification.

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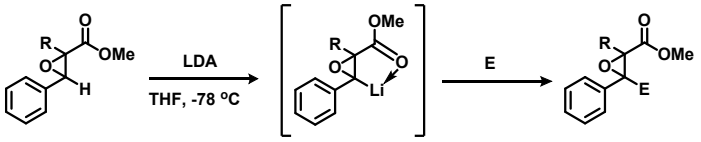
formed,

Table 2. Lithiation and substitution of epoxy cinnamates **5** and **6**.



5 : R = Me
6 : R = Ph

7 : R = Me
8 : R = Ph

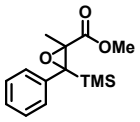
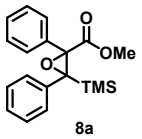
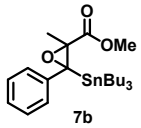
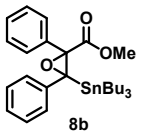
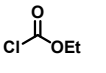
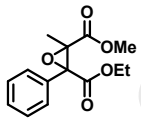
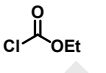
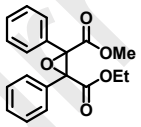
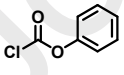
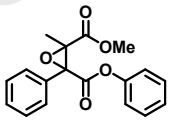
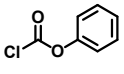
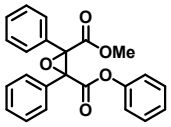
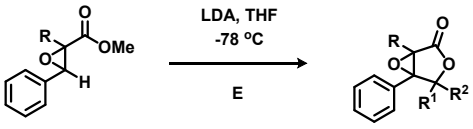
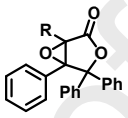
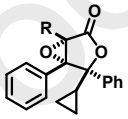
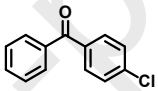
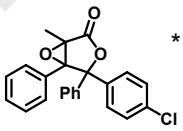
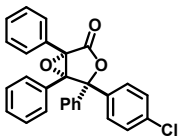
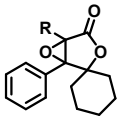
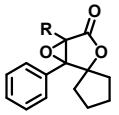
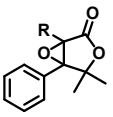
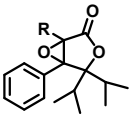
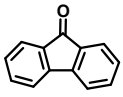
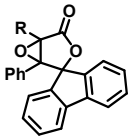
Entry	(R)	Electrophile (E)	Product	% Yield	% Recovery
1	Me	TMSCl	 7a	46	-
2	Ph	TMSCl	 8a	54	-
3	Me	Bu_3SnCl	 7b	42	11
4	Ph	Bu_3SnCl	 8b	48	14
5	Me		 7c	42	5
6	Ph		 8c	48	12
7	Me		 7d	51	18
8	Ph		 8d	30	24

Table 3. Synthesis of α,β-epoxy-γ-butyrolactones **7** and **8**.



5 : R = Me
6 : R = Ph

7 : R = Me
8 : R = Ph

Entry	Electrophile (E)	Product	% Yield	% Recovery
1			7e ; 41 8e ; 43	21 19
2			7f ; 19 8f ; 23	15 21
3		 **	7g ; 53	12
			8g ; 42	17
4			7h ; 30 8h ; 33	18 14
5			7i ; 29 8i ; 29	24 15
6			7j ; 29	22
7			7k ; 28 8j ; 33	18 23
* 8			7l ; 31 8k ; 8	- 18

* LTMP was used as a base in the lithiation step.
** The reaction gave the diastereomeric mixture.

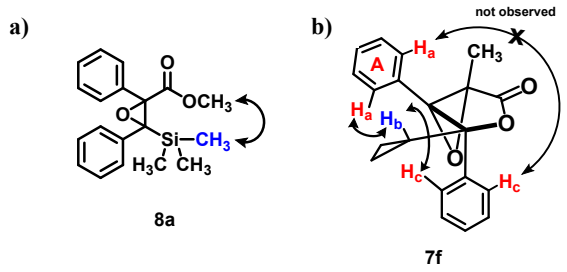
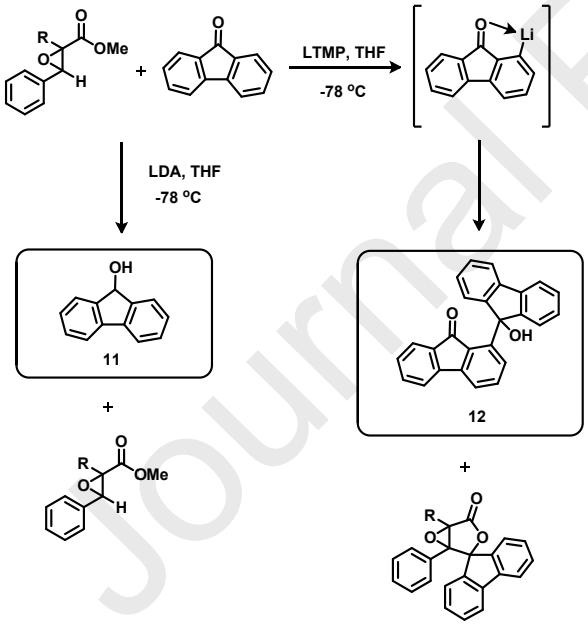


Figure 2. Key NOE correlations of compounds a) **8a** and b) **7f**.

it was unable to be isolated by this purification method. The relative stereochemistry of **7f** could be assigned by selective NOE correlations as shown in Figure 2b. Irradiation of the cyclopropyl proton at δ 1.69 ppm (H_b) enhanced the other cyclopropyl protons at δ 0.50 ppm and 0.85 ppm, as well as the phenyl protons at δ 6.80 ppm (H_a) and 7.10 ppm (H_c). However, irradiation of H_a enhanced H_b, but not H_c. This result suggested that the cyclopropyl group was located on the same side as the phenyl ring A.[18]

Unfortunately, the reaction of epoxides **5** and **6** with fluorenone as an electrophile in the presence of LDA provided only the reduced product fluorenol **11**, without any of the desired product (Scheme 5).[19] To avoid the reduction, lithium 2,2,6,6-tetramethylpiperidide (LTMP) was applied to generate the lithiated anion and further reacted with fluorenone to afford the desired products **7l** and **8k**. Surprisingly, keto-alcohol **12** was also observed due to the *ortho*-lithiation of fluorenone (Scheme 5).[20]



Scheme 5. Reaction of the oxiranyl remote anions of α,β-epoxy cinnamate derivatives with fluorenone.

In conclusion, an investigation of the oxiranyl remote anions derived from α,β-epoxy cinnamate derivatives and their reactions with variety of electrophiles were described. Chelation between the lithium atom and an ester group *via* a five-membered cyclic intermediate plays a key role in the stabilization of the anion. The oxiranyl remote anions of an ester could be applied in the preparation of various α,β-epoxy-γ-butyrolactones, a useful as electrophiles.

Acknowledgments

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Supplementary data

Synthetic procedures and supplementary data (^{1}H and ^{13}C NMR spectra of compounds **7a-l**, **8a-k**, **9** and **10**) associated with this article can be found, in the online version, at doi:XXXXXXXXX.

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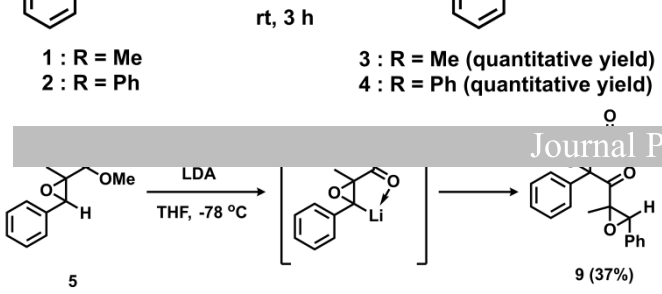

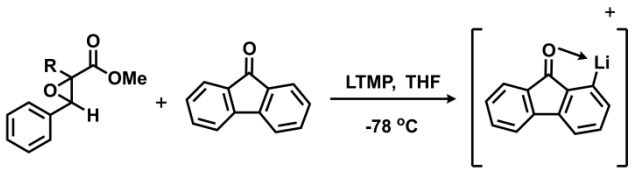

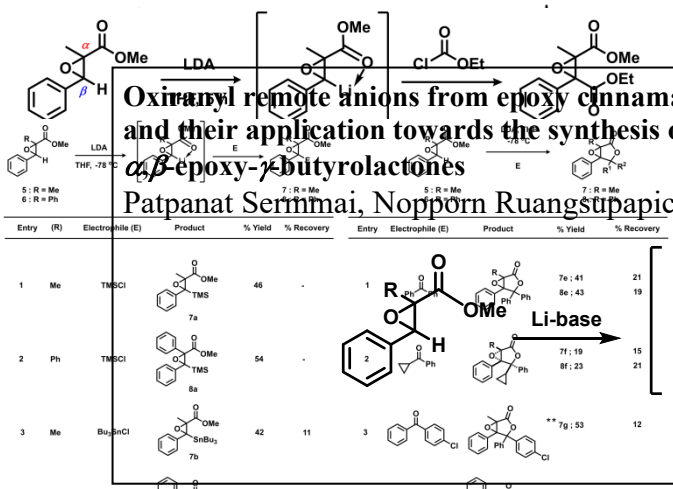

Highlights

- β-anion of an epoxy cinnamate could be generated and stabilized by its ester group.
- The generated anion could react with various electrophiles, including ketones.
- α,β-epoxy-γ-butyrolactones could be prepared by this novel remote anion chemistry.

Oxiranyl remote anions from epoxy cinnamates and their application towards the synthesis of α,β-epoxy-γ-butyrolactones

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* LTMP was used as a base in the lithiation step.
** The reaction gave the diastereomeric mixture.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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