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Diastereoselective synthesis of γ-hydroxy α,β-epoxyesters and their conversion into β-hydroxy α-sulfenyl γ-butyrolactones

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Abstract—The diastereoselectivity of the nucleophilic epoxidation of γ-hydroxy-α,β-unsaturated esters has been studied. The γ-hydroxy-α,β-unsaturated esters were obtained through treatment of ethyl (*E*)-4-oxo-2-butenoate with the corresponding Grignard reagent and were used as a racemic mixture. The resulting γ-hydroxy α,β-epoxyesters were treated with thiophenol for transformation into α-phenylsulfanyl trisubstituted γ-butyrolactones. The *syn*,*syn*-lactones isomerize easily in basic media into the *syn*,*anti* structures. In order to explain this interconversion, a retroaldol–aldol sequence has been proposed and a sulfur–oxygen interaction has been invoked to explain the *syn* stereochemical preference of the α-sulfured aldols resulting from the intramolecular aldol reaction.

1. Introduction

α,β-Epoxyesters are versatile functionalities in organic synthesis since they can be converted into interesting synthetic compounds through the opening of the oxirane ring.[1] The most convenient method for their preparation is through epoxidation of unsaturated esters using a hydroperoxide in the presence of a base.[2] A deeper understanding of the stereoselectivity of the epoxidation of unsaturated esters would increase the synthetic applications of these intermediates. We previously reported the influence of solvent and temperature on the epoxidation of γ-hydroxy-α,β-unsaturated esters[3] and now wish to report a general study of this reaction including a correction of the previous stereochemical assignment of some of the resulting epoxides.

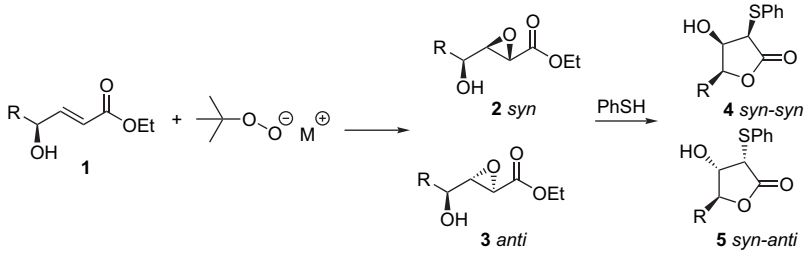
In this paper we also show that the thiophenol-mediated transformation of the γ-hydroxy α,β-epoxyesters into α-phenylsulfanyl γ-butyrolactones **4/5** was useful for the stereochemical determination of the preceding epoxyesters (Scheme 1). Trisubstituted γ-butyrolactones are an interesting family of compounds,[4] which could be then obtained starting from chiral γ-hydroxy α,β-epoxyesters.

The stereoselectivity of the epoxidation reactions was measured as the ratio between *syn*/*anti* diastereomers **2** and **3** (Scheme 1) and must be interpreted as a conjugate addition to an unsaturated ester modulated by a stereocenter in the γ-position.[5]

2. Results

2.1. Preparation of substrates

We wanted to study the selectivity of epoxidation of γ-hydroxy-α,β-unsaturated esters with a range of R alkyl



Scheme 1. General scheme of reactions.

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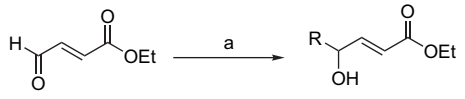
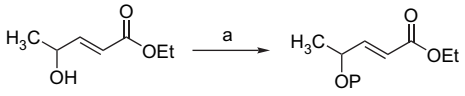
groups. Commonly γ-hydroxy-α,β-unsaturated esters are obtained in enantiopure form through Wittig–Horner reaction of chiral aldehydes or enzymatic resolutions of the corresponding racemic mixtures,[6] we synthesized the γ-hydroxy-α,β-unsaturated esters through treatment of ethyl (*E*)-4-oxo-2-butenoate[3] with the corresponding Grignard reagent and they were used as a racemic mixture in the epoxidation process (Scheme 2).



1a, R=Ph
1b, R=Me
1c, R=*i*-Propyl
1d, R=*i*-Pentyl
1e, R=*n*-Butyl
1f, R=Chx
1g, R=*p*-MeOPh
1h, R=*t*-Butyl

Scheme 2. Preparation of γ-hydroxy-α,β-unsaturated esters: (a) RMgBr, THF, −78 °C–0 °C.

We also prepared *O*-protected α,β-unsaturated esters in order to study the influence of the hydroxyl protecting group on the epoxidation. These compounds were synthesized through protection of compound **1b** via standard conditions (Scheme 3).



1b

6a, P=TPS
6b, P=TIPS
6c, P=MOM

Scheme 3. Protection of γ-hydroxy-α,β-unsaturated esters: (a) P–Cl, base.

2.2. Epoxidation of γ-hydroxy-α,β-unsaturated ethyl esters

Esters **1** were epoxidized using lithium *tert*-butylperoxide as the oxidizing reagent in THF as solvent at −20 °C. Table 1 shows that the diastereomeric ratios are similar for all conditions examined, furnishing the **2** *syn* isomer as the major product. The *syn*/*anti* assignment for **2b/3b** represents a correction to our previous work,[3] an explanation for which is provided subsequently.

These results showed that stereoselectivity does not depend on the nature of the pendant R alkyl group for all γ-hydroxy-α,β-unsaturated esters examined.

In order to study the influence of the temperature over the stereoselectivity, we carried out the epoxidation reaction of compound **1b** at different temperatures (Table 2).

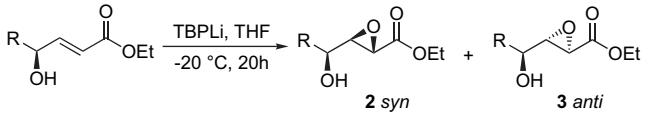
Table 2 shows that there is no temperature dependence since the diastereomeric ratios at different temperatures in a range between −80 and 50 °C are same within experimental error.

Similar $J_{3,4}$ coupling constants were observed for diastereomers *syn* α,β-epoxyesters **2a–h** and also for *anti* α,β-epoxyesters **3a–h** (Table 3). For *syn* isomers, $J_{3,4}$ values were between 3.5 and 4.5 Hz whilst for the *anti* form, $J_{3,4}$ ranged from 2.5 to 3.5 Hz.

Thus, the measurement of $J_{3,4}$ represented a convenient method for the stereochemical assignment of these compounds whenever both isomers were available.

We also epoxidized compound **1b** by using oxidants other than lithium *tert*-butylperoxide (Table 4).

Table 1. Epoxidation of γ-hydroxy-α,β-unsaturated esters using lithium *tert*-butylperoxide

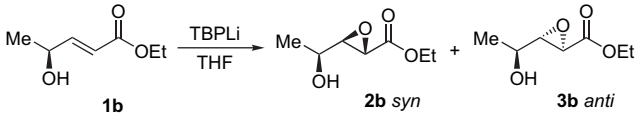


2 *syn* **3** *anti*

Entry	Substrate	R	*T* (°C)/*t* (h)	**2**:**3**[a]	Yield (%)
1	**1a**	Ph	−20/20	80:20	78
2	**1b**	Me	−20/20	70:30	60
3	**1c**	*i*-Pr	−20/20	80:20	55
4	**1d**	*i*-Pent	−20/20	78:22	44
5	**1e**	*n*-Bu	−20/20	81:19	48
6	**1f**	Chx	−20/15	76:24	47
7	**1g**	*p*-MeOPh	−20/15	77:23	69
8	**1h**	*t*-Bu	−20/72	70:30	41

[a] Ratio measured by ^{13}C NMR of the crude reaction mixtures.

Table 2. Epoxidation of **1b** at different temperatures

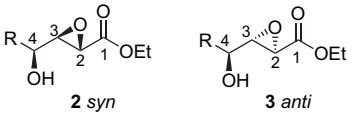


1b **2b** *syn* **3b** *anti*

Entry	*T* (°C)/*t* (h)	**2b**:**3b**[a]	Yield (%)
1	−80/72	73:27	30
2	−60/46	78:22	55
3	−40/24	77:23	54
4	−20/20	70:30	60
5	0/14	74:26	55
6	25/3	78:22	52
7	50/5	76:24	45

[a] Ratio measured by ^{13}C NMR of the crude reaction mixtures.

Table 3. Coupling constants of epoxyalcohols



2 *syn* **3** *anti*

R	$J_{3,4}$ **2** *syn* (Hz)	$J_{3,4}$ **3** *anti* (Hz)
Ph	4.5	2.5
Me	4.2	3.1
i-Pr	4	3
i-Pent	4	3.5
n-Bu	4	[a]
Chx	4	3
p-MeOPh	4.5	2.5
t-Bu	3.5	2.5

[a] Coupling constant could not be measured because of overlapping signals.