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First lipase catalysed resolution of epoxy enol esters

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Abstract—We report the first enzyme-catalysed kinetic resolution of epoxy enol esters. The lipase-promoted hydrolysis of these compounds provided α-hydroxyketones or α-hydroxyaldehydes (arising from the spontaneous rearrangement of the epoxy enols) and the residual esters with moderate to good enantioselectivity (*E* up to 100).

1. Introduction

α-Hydroxyaldehydes are valuable synthetic intermediates and are also building blocks for the synthesis of carbohydrates and analogues via chemical or enzymatic aldol reactions.[1] As part of a research program designed to explore the utility of transketolase and fructose-1,6-bisphosphate aldolase in organic synthesis, we required a number of chiral α-hydroxyaldehydes preferably in the enantiomerically pure form.[2] α-Hydroxyaldehydes are generally accessible by two main routes. First, a general method based on the ozonolysis of allylic alcohols provides the aldehyde functionality. Enantiomerically enriched allylic alcohols can be obtained by enzymatic resolution.[3] Alternatively, α-hydroxyaldehyde acetals are obtained, either by the ring opening of a 2,3-epoxy-propionaldehyde-diethylacetal by various nucleophiles or by a Barbier type reaction on a glyoxal monoacetal.[4] The acetals are then readily hydrolysed in acidic media. α-Hydroxyaldehydes often present as oligomers are very difficult to purify and characterise so that the last step of their synthesis has to be very efficient and must not generate by-products. However, in the first method, the reductive work-up after hydrolysis produces either triphenylphosphine oxide or dimethylsulfoxide, and in the second method, the acidic conditions required for acetal hydrolysis can lead to partial racemisation or isomerisation into α-hydroxyketones.

Therefore, the preparation of chiral α-hydroxyaldehydes remains an issue and we looked for alternative enzymatic methods to generate these compounds under mild conditions. In 1996, Kern and Spiteller[5] reported the synthesis of three racemic long chain aliphatic α-hydroxyaldehydes by a thermal rearrangement of epoxy enol esters in the presence of a protic acid, followed by enzymatic hydrolysis of the intermediate α-acetoxyaldehydes (Scheme 1). More recently, Shi and co-workers.[6] showed that the rearrangement of enol ester epoxides to α-acyloxy ketones under thermal or acidic conditions is stereoselective.

It occurred to us that direct enantioselective enzyme catalysed hydrolysis of epoxy enol acetates could provide optically pure α-hydroxyaldehydes or a α-hydroxyketones via an unstable hemiketal, and residual epoxy enol acetates.

Herein, we report which are, to the best of our knowledge, the first enzyme-catalysed resolutions of epoxy enol esters (also called enol ester epoxides) to give enantiomerically enriched α-hydroxyaldehydes or α-hydroxyketones.

2. Results and discussion

2.1. Synthesis of substrates

We prepared racemic enol ester epoxides **1**, **2**, **3a–c** (Fig. 1) by two different routes. Compounds **1** and **2** can lead to α-hydroxyketones whereas compounds **3a–c** are precursors for α-hydroxyaldehydes. Also, it is

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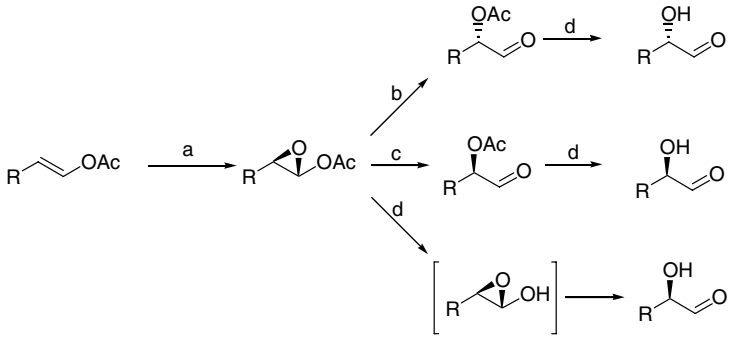


Scheme 1. Synthesis of α-hydroxyaldehydes from enol acetate epoxides: (a) epoxidation, (b) thermal or Lewis acid catalysed rearrangement, (c) protic acid catalysed rearrangement, (d) enzymatic hydrolysis.

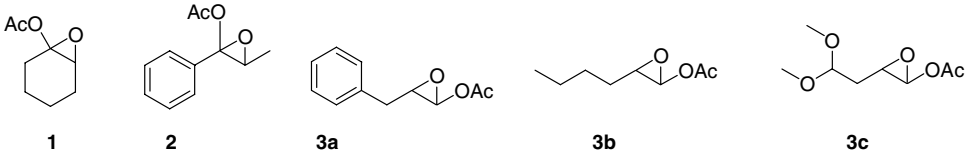
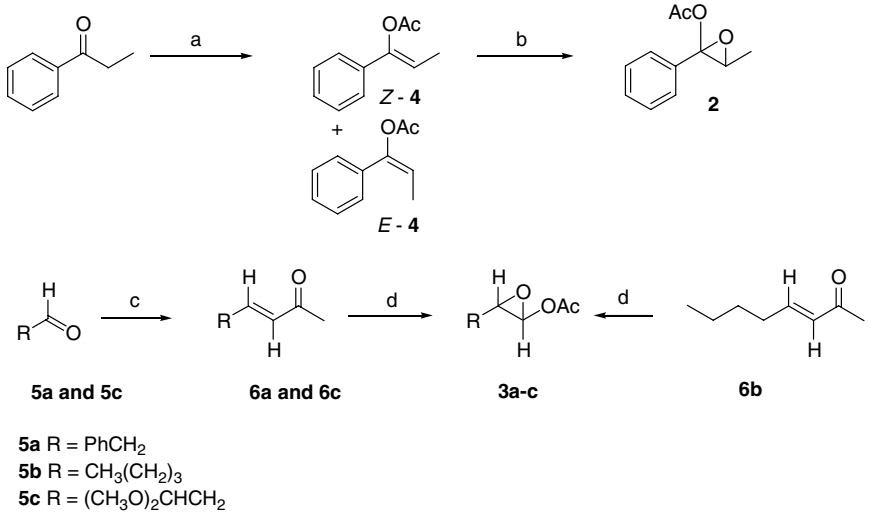


Figure 1. Epoxy enol ester substrates.

necessary to control the *E*–*Z* configuration of acyclic compounds **2**, **3a**–**c** since the presence of the two diastereoisomers will decrease the enantiomeric purity of the desired hydroxyaldehydes or hydroxyketones.

According to a reported procedure,[7] 1-acetoxy-1,2-epoxycyclohexane **1** was prepared from cyclohexanone by acylation with isopropenyl acetate in the presence of *p*-toluenesulfonic acid (*p*-TsOH) as a catalyst followed by epoxidation of the intermediate cyclohexanone enol acetate by *m*-chloroperbenzoic acid (MCPBA). 1-Acetoxy-1,2-epoxy-1-phenylpropane **2** was obtained by a similar two-step procedure (Scheme 2). Propiophenone enol ester **4** was prepared from propiophenone and acetic anhydride using *p*-TsOH as a catalyst with a 43% yield. The isomeric ratio $Z/E = 10$ was determined by gas chromatography and a flash column chromatography afforded pure *Z*-**4**. The epoxidation of this isomer was carried out with MCPBA (74% yield).

We then applied the above method based on the epoxidation of enol esters to the preparation of compounds **3a**–**c** but inseparable mixtures of *E*–*Z* isomers were obtained. We therefore examined another way of controlling the stereochemistry of the products, starting from α,β-unsaturated ketones **6a**–**c** (Scheme 2). Compound **6b** is commercially available, **6a** and **6c** were prepared from aldehydes **5a** and **5c** by the Wittig reaction with 1-triphenylphosphoranylidene-2-propanone in 58% and 79% yield, respectively. It is generally found that ylides



Scheme 2. Synthesis of **2**, **3a**–**c**. Reagents and conditions: Ac_2O, *p*-TsOH, 165 °C, 12 h, $Z/E = 10$, 9% yield for *Z* isomer after purification; (b) MCPBA, CH_2Cl_2, 1 h, 0 °C, 3 h room temperature, 74% yield; (c) $Ph_3P{=}CHCOCH_3$, THF, room temperature. Compound **6a**, 6 days, 58%; **6c**, 12 h, 79%; (d) MCPBA, CH_2Cl_2, room temperature. Compound **6a**, 2 days 47%, **6b**, 5 days, 68%, **6c**, 3 days, 35%.

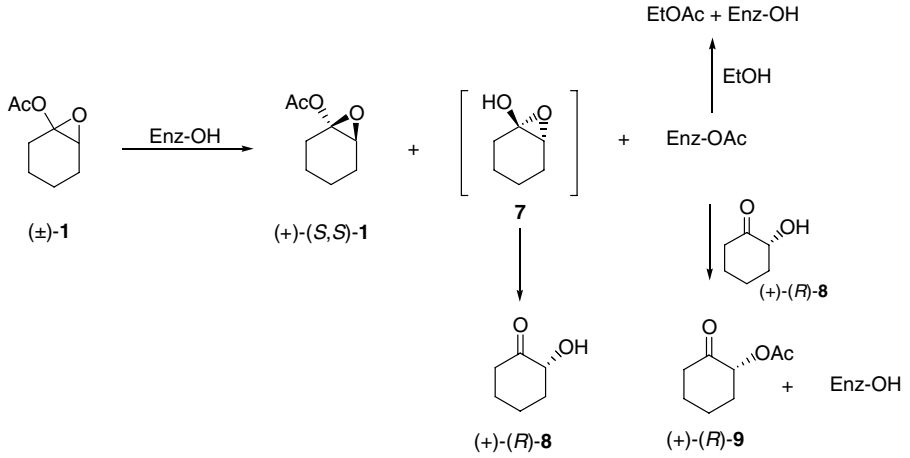
containing stabilising groups give *E* alkenes.[8] The *E* configuration was confirmed by ^{1}H NMR analysis of the olefinic protons and no *Z* isomer was detected. The tandem Baeyer–Villiger oxidation–epoxidation[9] of α,β-unsaturated ketones **6a–c** with an excess of *m*-chloroperbenzoic acid provided enol ester epoxides **3a–c** (47%, 68% and 35% yield). The Baeyer–Villiger reaction has been demonstrated to occur with retention of configuration.[10] The *E* (trans) configuration of the oxirane ring was confirmed by ^{1}H NMR analysis; a small coupling constant ($J \leqslant 1$ Hz) is expected for H-1 in the *E* (trans) configuration whereas $J \geqslant 3$ Hz is found in compounds with the *Z* (cis) configuration.[5] Dimethoxypropanal **5c** was obtained by ozonolysis of 4,4′-dimethoxybutene.[11]

2.2. Enzymatic kinetic resolutions

In this preliminary study, in order to demonstrate the validity of our approach, we studied the hydrolysis of **1**, **2**, **3a–c** in the presence of a few common commercial enzymes.[12]

Stereoselective enzymatic hydrolyses of esters can be carried out in aqueous buffers, in biphasic mixtures of water and an organic solvent, and in water saturated organic solvents; an alternative is the transesterification (alcoholysis) in a solvent of low polarity containing a simple alcohol.[13]

1-acetoxy-1,2-epoxycyclohexane **1** was chosen as the model substrate to investigate the kinetic resolution process. This compound is unstable in the presence of water and we operated in diisopropyl ether containing 1% ethanol. The resolution was carried out on 1 mmol of substrate, 200 mg of enzyme in 3 ml of solvent. The results are reported in Scheme 3 and Table 1. The enantioselective reaction of (±)-**1** in the presence of various lipases gave α-hydroxyketone (*R*)-**8**, a small amount of the corresponding α-acetoxyketone (*R*)-**9**, and the residual starting material (1*S*,2*S*)-**1**. The progress of the reaction c (conversion rate) was monitored by gas chromatography. Comparison of the specific rotation of chiral nonracemic **1** with data reported in the literature[6] established its optical purity and its absolute configuration. The stereochemistry of the reactions was further confirmed by the optical rotation data of known (*R*)-(+)-2-hydroxycyclohexanone **8**.[14] The enantiomeric ratio *E*[15] was measured using the extent of conversion *c* and the optical purity of the starting material. The reaction mechanism is shown in Scheme 3. Alcohol **8** results from the rearrangement of hemiacetal **7** provided by the enzymatic ester hydrolysis or alcoholysis. The formation of acetoxycyclohexanone **9** can be due to the esterification of **8**. Indeed lipases are able to acylate alcohols in nonaqueous solvents in the presence of acyl group donors, here the substrate **1**. During the reaction, an intermediate acetyl-enzyme is formed, which undergoes an



Scheme 3. Enzymatic alcoholysis of 1-acetoxy-1,2-epoxycyclohexane **1**.

Table 1. Enzymatic alcoholysis/hydrolysis of 1-acetoxy-1,2-epoxy cyclohexane **1** in diisopropyl ether

Entry	Enzyme[a]	Conditions[b]	Time (h)	*c*[c] (%)	Product ratio 1/8/9	Residual **1** optical purity (%)[d]	*E*
1	CAL	EtOH 1%	192	56	44/36/20	71	7.2
2	PSL	EtOH 1%	26	53	47/45/8	82	15
3	PSL		48	60	40/35/25	83	8.6
4	CRL	EtOH 1%	17.5	50	50/45/5	90	40
5	CCL		96	59	41/34/25	98	23
6	CCL	EtOH 1%	32	59	40/42/18	88	11
7	CCL	H2O satd	7	55	45/45/10	92	22

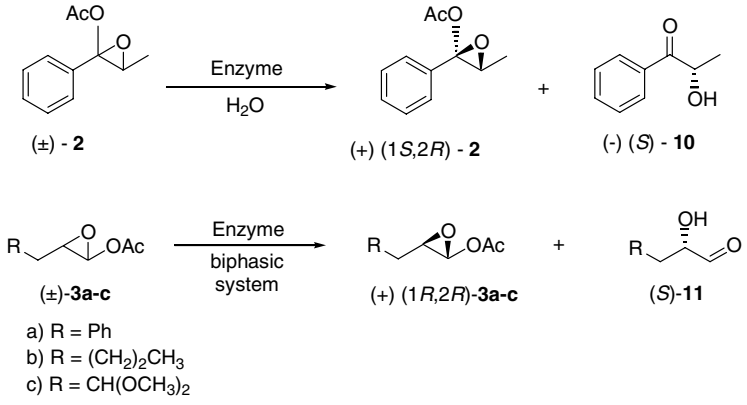
[a] CAL: *Candida antarctica* lipase B; PSL: *Pseudomonas* sp. lipase; CRL: *Candida rugosa* lipase; CCL: *Candida cylindracea* lipase.
[b] 1 mmol (156 mg) of substrate, 200 mg of lipase in 3 ml of diisopropyl ether.
[c] After isolation of products.
[d] Optical purity according to literature data.

hydrolysis, or in the absence of water an alcoholysis by added ethanol or alcohol **8**. When no EtOH was added (assays 3 and 5), residual water present in the enzyme preparation and hydroxycyclohexanone **8** were the nucleophiles competing in the enzyme regeneration and the yield in **9** increased.

1-Acetoxy-1,2-epoxy-1-phenylpropane **2** reacts very slowly in organic media and is stable in a phosphate buffer pH 7. Thus, the hydrolysis was carried out on 1 mmol of substrate in 50 ml of this buffer in the presence of 27 mg of enzyme, or in a biphasic system hexane (30 ml)/phosphate buffer (30 ml) in the presence of 2 mg of enzyme. The results are summarised in Scheme 4 and Table 2. The enantiomeric excesses and the absolute configurations were determined by comparison with literature data; the absolute configurations of residual (+)-**2**[6] and (−)-2-hydroxy-1-phenylpropan-1-one **10**[16] are (1*S*,2*R*) and (*S*), respectively. Lipases from *Pseudomonas* sp. (PSL), *Candida cylindracea* (CCL) and *Candida rugosa* (CRL) showed very low enantioselectivity towards substrate **2**. The best results were obtained with *Candida antarctica* lipase B (CAL) in phosphate buffer ($E = 34$).

Next, we completed some screening experiments in order to find hydrolases with the ability to resolve enol ester epoxides **3a**–**c** leading to α-hydroxyaldehydes. Of the enzymes and conditions tested, the hydrolysis of **3a**–**c** (1 mmol) in a biphasic system buffer/hexane in the presence of CAL (2 mg) gave the best results (Scheme 4 and Table 2). In all hydrolysis reactions, the (*S*,*S*) enol ester epoxide was the fast reacting enantiomer yielding the (*S*)-hydroxyaldehyde (vide infra) and leaving the (*R*,*R*)-epoxide unreacted in enantiomerically enriched form. The formation of α-acetoxyaldehydes was not observed with these substrates. The enantiomeric excess of the remaining epoxides were measured by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent (substrates **3a** and **3c**) or by chiral gas chromatography on a chiraldex γ-TFA column (substrate **3b**). The enantiomeric compositions and absolute configurations of aldehydes **11a**–**c** were determined by conversion to the corresponding dimethylacetals **12a**–**c** (in the case of **11c**, a transacetalation produced the bis-dimethylacetal) followed by ^{19}F and ^{1}H analysis[17] of the Mosher's esters (α-methoxy-α-trifluoromethyl-α-phenyl acetates **13a**–**c**) (Scheme 5). The absolute configurations of **11a** and **11c** were further confirmed by correlation with 1,2-diol **14a**[18] and **14c**[19] of known absolute configuration.

In conclusion, we have developed the first biocatalytic kinetic resolution of enol ester epoxides leading to homochiral enol ester epoxides and α-hydroxyaldehydes or α-hydroxyketones. Enol ester epoxides are synthetically useful intermediates. One enantiomer (1*R*,2*R*) in the case of **3a**–**c** can be obtained in a good enantiomeric excess. The reacting enantiomers (1*S*,2*S*) in the case of

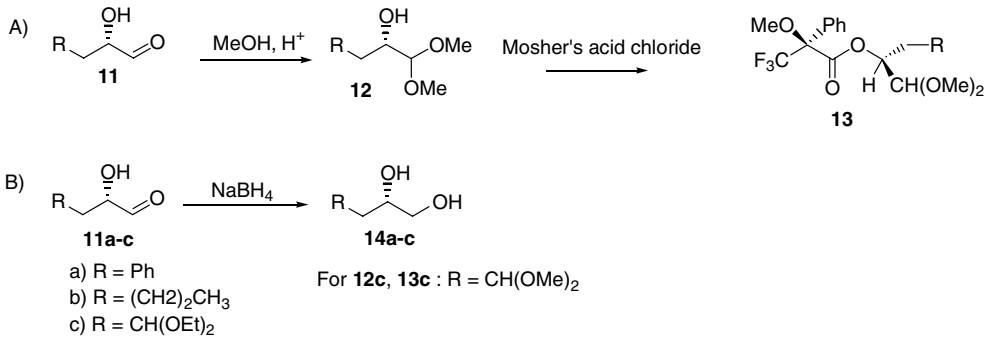


Scheme 4. Enzymatic hydrolysis of epoxy enol esters **2** and **3a**–**c**.

Table 2. Enzymatic hydrolysis of epoxy enol esters **2**, **3a**–**c**

Entry	Substrate	Conditions	Enzyme	Time (h)	C[e] (%)	ee or (op) of residual substrate (%)	E
1	**2**	Buffer[a]	CAL[b]	17		(92)	34[c]
2	**2**	Buffer[a]	PPL[b]	18		(50)	9[c]
3	**2**	Buffer/hexane[d]	CAL	31	56	(93)	21[e]
4	**3a**	Buffer/hexane[d]	CAL	1	62	46	15
5	**3b**	Buffer/hexane[d]	CAL	4	46	89	100
6	**3b**	Buffer/hexane[d]	PSL[b]	24	47	88	75
7	**3c**	Buffer/hexane[d]	CAL	11	64	96	12

[a] 1 mmol (228 mg) of substrate in 50 ml of phosphate buffer pH 7, 27 mg of enzyme.
[b] *Candida antarctica* lipase; PPL: Porcine pancreatic lipase; PSL: *Pseudomonas* sp. Lipase.
[c] Calculated from the optical purity of isolated residual substrate and product.
[d] 1 mmol of substrate (228, 240, 158 and 190 mg of **2**, **3a**–**c**) in 30 ml of hexane and 30 ml of phosphate buffer (0.1 M, pH 7) containing 2 mg of enzyme.
[e] Determined by GC analysis.



Scheme 5. Determination of enantiomeric excesses and absolute configuration of **11a–c**.

3a–c lead to the (2*S*) α-hydroxyaldehydes of good enantiomeric excess if the hydrolysis is stopped before 50% conversion (depending of the *E* value). On the other hand, the residual epoxides can be hydrolysed under mild conditions in the presence of a nonspecific esterase (like pig liver esterase or pig pancreatic lipase (Table 2)) to lead to (2*R*) α-hydroxyaldehydes. Moreover, residual ester enol epoxides can be submitted to a stereoselective rearrangement with retention or inversion of configuration to provide either enantiomer of α-acyloxy aldehydes or ketones.[6] By this methodology, both isomers of α-hydroxyaldehydes, which are prone to racemise or isomerise into hydroxyketone can be obtained in aqueous solution at neutral pH. The scope and limitations of this novel biocatalytic reaction and its synthetic application are currently being studied in detail.

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