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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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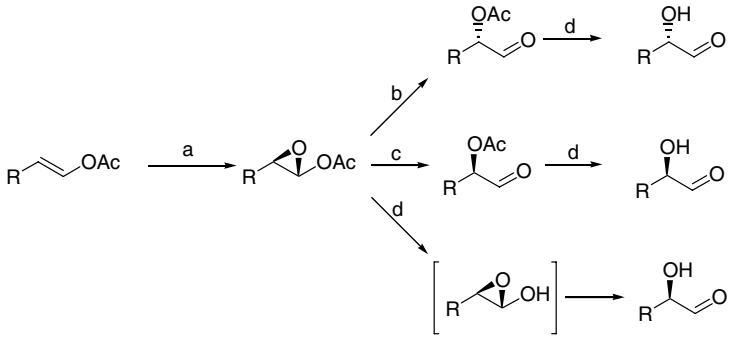


Scheme 1. Synthesis of α-hydroxyaldehydes from enol acetate epoxides: (a) epoxidation, (b) thermal or Lewis acid catalysed rearrangement, (c) protic acid catalysed rearrangement, (d) enzymatic hydrolysis.

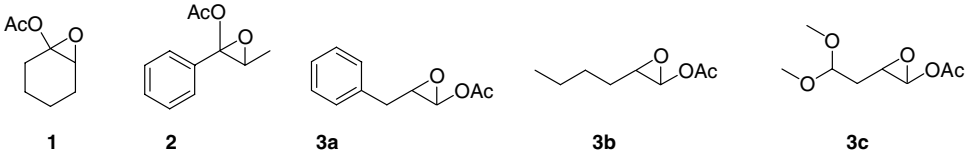
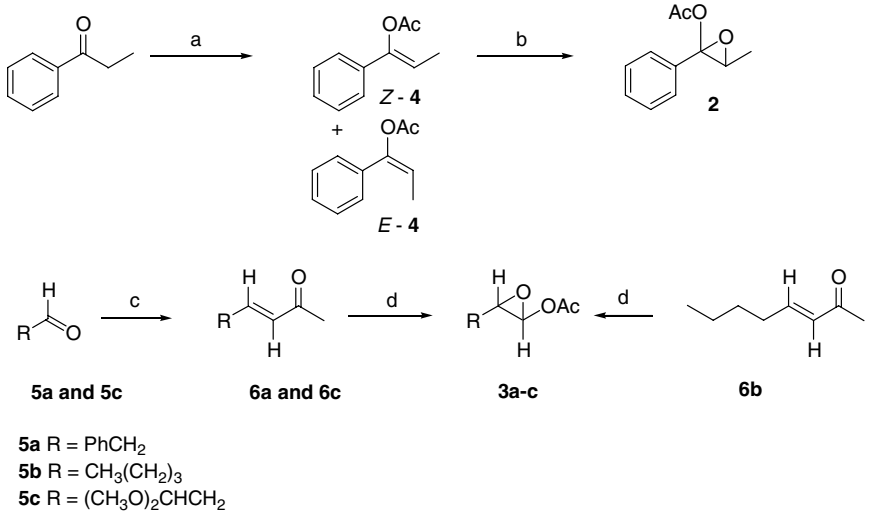


Figure 1. Epoxy enol ester substrates.

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%.