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A New and Efficient Chemoenzymatic Route to Both Enantiomers of 4-Hydroxycyclohex-2-en-1-one

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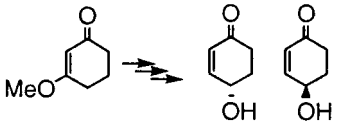
ABSTRACT



A chemoenzymatic synthesis of both enantiomers of the pharmacologically interesting 4-hydroxycyclohex-2-en-1-one in three steps starting from 3-methoxycyclohex-2-en-1-one is described. Manganese(III) acetate-mediated acetoxylation followed by enzyme-mediated hydrolysis of α-acetoxy enone affords acetoxy enone 3 and hydroxy enone 4 with high enantiomeric excesses and in good yields. The reduction of the acetoxy and hydroxy enones furnished both enantiomers of 4-hydroxycyclohex-2-en-1-one in high enantiomeric excess.

Chiral α-hydroxy ketones are important structural units in many biologically active compounds, and they are also important synthons for the asymmetric synthesis of natural products.[1] During the past several years, there has been an increasing interest in the biological and pharmacological properties of members of the compactin−mevinolin family of natural products,[2] koninginine,[3] phyllanthurino lactone and related compounds.[4] Optically active 4-hydroxycyclohex-2-en-1-one (**1**) has been employed in several laboratories as a starting material for the synthesis of such kinds of compounds. It is, therefore, of considerable interest to develop efficient methods for preparing optically active 4-hydroxycyclohex-2-en-1-one (**1**) that minimize the number of required synthetic steps while maximizing the overall chemical and optical yield of this important intermediate.

Several preparations of (*S*)-**1** and (*R*)-**1** have been published by using either chemical[5] or enzymatic[6] transformations. Many of these syntheses involve multistep sequence with low overall yields and poor enantioselectivities. Danishefsky and co-workers developed a multistep procedure for the preparation of (*S*)-**1** from a homochiral natural product, quinic acid.[5a] Starting from the same acid, Brückner et al. reported the synthesis of the other enantiomer, (***R***)-**1**, in six steps with 18% overall yield and 100% enantiomeric

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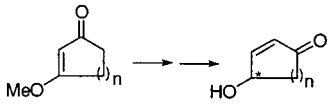
purity.[5d] The bakers' yeast-mediated monoreduction of a diketone possessing the structure of a Diels−Alder adduct of 2-cyclohexene-1,4-dione and cyclopentadiene and a subsequent [4 + 2] cycloreversion gave (*S*)-4-hydroxycyclohex-2-en-1-one with 67% ee.[6a] Kazlauskas et al. described the enzymatic hydrolysis of the two diastereomeric Br_2 adducts of *cis*-3,6-diacetoxy-1-cyclohexene followed by sequential treatment with Zn and Collins' reagent which gave (*S*)-4-acetoxycyclohex-2-en-1-one in 97% ee.[6b] Starting from *cis*-3,6-diacetoxy-1-cyclohexene, Kibayashi et al. synthesized (*R*)- and (*S*)-**1** in 88% ee via enzyme-catalyzed desymmetrization reaction.[6c]

In our ongoing work, we have published several papers about the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation (carried out via metathesis of acetic acid by various carboxylic acids) of enones and aromatic ketones followed by the enzyme- and fungus-mediated resolution of acyloxy enones to obtain optically pure α-hydroxy ketones.[7] The great importance of chiral 4-hydroxycyclohex-2-en-1-one (**1**) led us to explore a chemoenzymatic method for obtaining them in enantiomerically pure form, and we describe herein an efficient chemoenzymatic route to the three-step synthesis of both enantiomers of **1** starting from 3-methoxycyclohex-2-en-1-one (**2**), which is a representative example for the simple enantioselective synthesis of cyclic 4-hydroxy enones (Scheme 1).

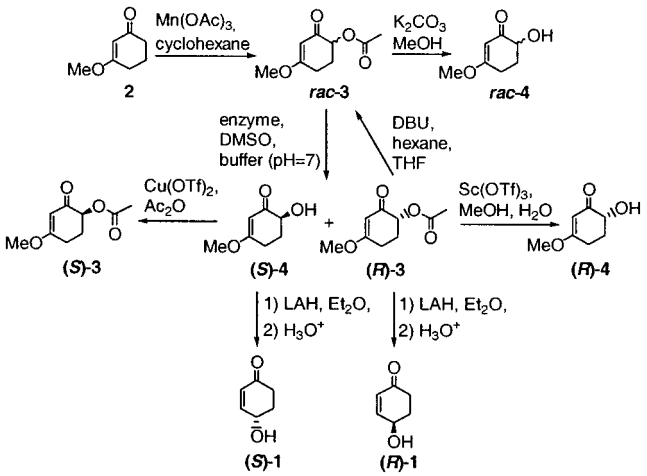
Scheme 1



Commercially available cyclohexane-1,3-dione was converted to the 3-methoxycyclohex-2-en-1-one (**2**) using a procedure reported in the literature.[8] As an initial reaction (Scheme 2), oxidation of enone **2** with 4 equiv of manganese(III) acetate in cyclohexane was performed to obtain the desired 6-acetoxy enone, *rac*-**3**, in 87% yield after purification by column chromatography. Use of benzene as a solvent also furnished the acetoxy enone (71%), however, with some undefined side products. Direct synthesis of acyloxy enone *rac*-**3** under mild conditions from enone **2** using manganese(III) acetate is an attractive alternative to the other (multistep) procedures for α′-oxidation.

Lipase type enzymes are used extensively for the synthesis of enantiomerically pure compounds via resolution of racemic mixtures. The high stereoselectivity in organic media

Scheme 2



and their low cost make them very useful catalysts for enantioselective resolution.

On the basis of the preliminary information available to us from our previous work with biocatalyst-mediated reactions,[7d,e,9] we tried a series of enzymes for screening the enantioselective hydrolysis of acetoxy enone *rac*-**3**. Ester hydrolysis of *rac*-**3** was investigated using four readily available enzymes: PLE (pig liver esterase), Amano PS, CCL (*Candida cylindracea* lipase), and PPL (porcine pancreatic lipase). Surprisingly, all enzymes affected the hydrolysis, with PLE and Amano PS exhibiting high enantioselectivity. Careful monitoring of the reactions with TLC and LC-MS furnished the acetoxy enone (***R***)-**3** (43−96% ee) and hydroxy enone (***S***)-**4** (55 → 98% ee) (Table 1).

Table 1. Enzymatic Hydrolysis of 6-Acetoxy-3-methoxycyclohex-2-en-1-one (**3**)

				acetate		alcohol		
no.	enzyme	reactn time (h)	convn c^a (%)	ee^b (%)	yield^c (%)	ee^b (%)	yield^c (%)	E^d
1	PLE	24	50	96	45	>98	47	195
2	Amano PS	22	50	95	41	96	45	146
3	CCL	24	52	60	51	55	43	6
4	PPL	23	37	43	54	75	37	11

[a] $c = ee_s/(ee_s + ee_p)$. [b] Determined by HPLC using chiral column (Chiralpak AD column, UV detection at 254 nm, eluent hexane/2-propanol= 9:1, flow 0.80 mL min^{-1} 20 °C, using racemic compounds as references). [c] Isolated yield after flash column chromatography. [d] Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

In a typical experiment, for enzymatic hydrolysis, the racemic acetoxy enone **3** was dissolved in DMSO (2 mL); then phosphate buffer (pH 7.0, 60 mL) was added and the mixture was stirred at room temperature in the presence of enzyme (1.5 mass equiv). The reaction was monitored by TLC analysis and LC-MS with a chiral column using acetoxy enone *rac*-**3** and hydroxy enone *rac*-**4** (synthesized from

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acetoxy enone *rac*-**3** with K_2CO_3/MeOH)[10] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford acetoxy enone (*R*)-**3** and hydroxy enone (*S*)-**4**. Best results were obtained using PLE and Amano PS. Termination of the PLE-catalyzed reaction after 52−54% conversion increases the ee of (*R*)-**3** to >98%. Absolute configuration determination of the products (*S*)-**4** and (*R*)-**3** was based on the absolute configuration of the known final product **1**.[5,6] Racemization-free acetylation of alcohol (*S*)-**4** was carried out with acetic anhydride/$Cu(OTf)_3$ according a procedure reported in the literature and (*S*)-**3** was obtained in 90% yield.[11] Likewise, racemization-free hydrolysis of chiral acetoxy enone was carried out with $Sc(OTf)_3$/MeOH−H_2O[12] and the reaction furnished (*R*)-**4** in 88% yield. Acetoxy enones obtained after bioconversion and acetylation reactions can be epimerized using DBU in hexane/THF[7e] to afford the racemic acetoxy enone **3** in 87−91% yields after purification by column chromatography. Recycling of the ester makes this method quite efficient for the enantioselective synthesis of the desired hydroxy enones. Hydroxy enone **1** is stable in a cold place under an inert atmosphere and away from light. The enantiomers of the hydroxy enone **1** with multifunctional groups are quite interesting starting materials for many biologically active compounds.

Since the reduction and hydrolysis of α′-acetoxy- or α′-hydroxy-α,β-unsaturated enone **3** and **4** provide access to γ-hydroxy-α,β-unsaturated enone,[13] the reaction of **3** and **4** with $LiAlH_4$ followed by acid-catalyzed hydrolysis and elimination furnished the desired product in 79−86% yield after separation of the crude product by column chromatography. The absolute configuration of the product was assessed by comparison of its specific rotation with data from the literature.[5,6] The chiroptical comparison and HPLC analysis of the products with racemic reference compounds using a chiral column showed that no isomerization occurred during this reaction. These results show that the reduction and elimination steps proceed with high selectivity. The reason for this behavior is still under investigation.

The results show that manganese(III) acetate-mediated acetoxylation of enone followed by enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enone (*S*)-**4** and acetoxy enone (*R*)-**3** with high enantiomeric excesses (>98%) and in good chemical yields. The undesired acetoxy enone can be epimerized in good yield and reused. In these conversion reactions, enzymes favor the (*S*)-enantiomers. The reduction of the acetoxy and hydroxy enone followed by acid hydrolysis furnished both enantiomers of 4-hydroxycyclohex-2-en-1-one **1** in high enantiomeric excess. This method gives a simple new entry to the synthesis of cyclic 4-hydroxy enones, which are important precursors for pharmacologically interesting compounds.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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