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TETRAHEDRON: *ASYMMETRY*

# A new and efficient chemoenzymatic access to both enantiomers of 4-hydroxycyclopent-2-en-1-one

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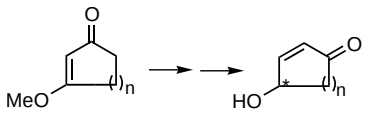
**Abstract**—A chemoenzymatic synthesis of both enantiomers of pharmacologically interesting 4-hydroxycyclopent-2-en-1-one in three steps starting from 3-methoxycyclopent-2-en-1-one is described. Manganese(III) acetate-mediated acetoxylation followed by enzyme-mediated hydrolysis of α-acetoxy enone affords 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-hydroxycyclopent-2-en-1-one in high enantiomeric excess. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

The enantiomers of 4-hydroxycyclopent-2-en-1-one (*S*)- and (*R*)-**1** have been the key starting materials for a variety of applications, most notably in one of the most popular routes to prostaglandins,[1] and the synthesis of natural products such as pentenomycin antibiotics[2] and ophiobolins,[3] as well as marine natural products such as clavulones,[4] antimicrobial diterpene, halimedatrial,[5] and antimicrobial and antileukemic didemnenones.[6] Several chemical and enzymatic methods have been described for the synthesis of both enantiomers of **1**.[7] We were interested to develop a chemoenzymatic procedure for the preparation of both isomers of **1**.

In our ongoing work we have published several papers about the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation of enones and aromatic ketones followed by the enzymatic- and fungus-mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones.[8] The great importance of the enantiomeric 4-hydroxycyclopent-2-en-1-ones **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-methoxycyclopent-2-en-1-one **2**, which is a representative example for the simple enantioselective synthesis of cyclic 4-hydroxy enones (Scheme 1).




**Scheme 1.**

## 2. Results and discussion

Commercially available cyclopentane-1,3-dione was converted to the 3-methoxycyclopent-2-en-1-one **2** using a procedure reported in the literature.[9] As an initial reaction (Scheme 2), oxidation of the enone **2** with manganese(III) acetate in cyclohexane was performed to obtain the desired 5-acetoxy enone, (±)-**3**, in 83% yield after purification by column chromatography.[10] The use of benzene as a solvent also furnished the acetoxy enone in 79% yield, however, with some side products.[11] Direct synthesis of acyloxy enone (±)-**3** under mild conditions from enone **2** using manganese(III) acetate is an attractive alternative to the other (multistep) procedures for the α′-oxidation. Lipase enzymes are used extensively for the synthesis of enantiomerically pure compounds via resolution of racemic mixtures. The high stereoselectivity in organic media and their low cost make them very useful catalysts for enantioselective resolution.

Based on the preliminary information available to us from our previous work with biocatalyst-mediated reactions,[8] we screened a series of enzymes for the enan-

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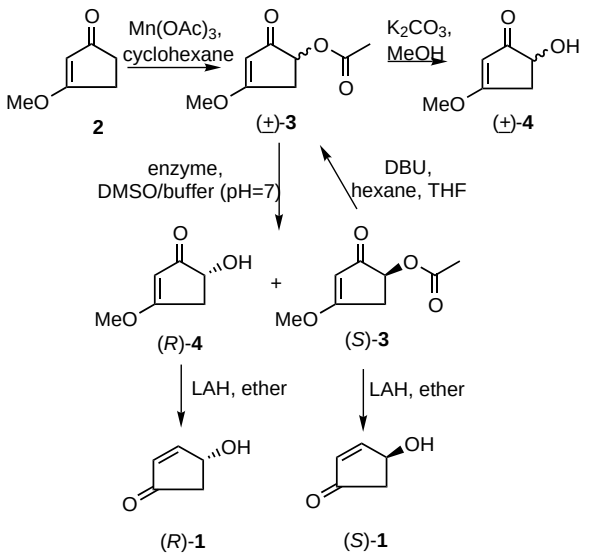


**Scheme 2.**

tioselective hydrolysis of acetoxy enone (±)-**3**. Ester hydrolysis of (±)-**3** was investigated using three readily available enzymes PLE (*Pig Liver* esterase), *Amano* PS, and PPL (*Porcine Pancreatic* lipase). Surprisingly, all enzymes affected hydrolysis, with PLE and *Amano* PS exhibiting high enantioselectivity, while PPL exhibits no selectivity. Careful monitoring of the reactions with TLC and LC–MS (Chiralpak AD column, UV detection at 254 nm, eluent: hexane/2-propanol = 9:1, flow 0.80 mL $min^{-1}$ 20°C, and Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.75 mL $min^{-1}$ 20°C, using racemic compounds as references) furnished the acetoxy enone (*S*)-**3** (96–97% e.e.) and hydroxy enone (*R*)-**4** (96–>98% e.e.) (Table 1).

In a typical experiment, for enzymatic hydrolysis, the racemic acetoxy enone **3** was dissolved in DMSO then phosphate buffer was added and the mixture was stirred at room temperature in the presence of enzyme. The reaction was monitored by TLC analysis and LC–MS with a chiral column using acetoxy enone (±)-**3** and hydroxy enone (±)-**4** (synthesized from acetoxy enone (±)-**3** with $K_2CO_3$/MeOH)[12] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford acetoxy enone (*S*)-**3** and hydroxy enone (*R*)-**4**. Best results were obtained on using PLE and *Amano* PS. Absolute configuration determination of the products (*R*)-**4** and (*S*)-**3** was based on the absolute configuration of the known final product **1**.[7a] Acetoxy enones obtained after bioconversion and acetylation reactions can be epimerized using DBU in hexane/THF[13] to afford the racemic acetoxy enone **3** in 85–90% yields after purification by column chromatography. Recycling of the ester makes this method quite efficient for the enantioselective synthesis of the desired hydroxy enones. The enantiomers of the enones (*S*)-**3** and (*R*)-**4** with multi functional 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 enones,[16] the reaction of **3** and **4** with $LiAlH_4$ followed by acid-catalyzed hydrolysis and elimination furnished the desired hydroxy enone **1** in 71–83% yields after separation of the crude product by column chromatography. The absolute configuration of the product was assessed by comparison of its specific rotation value with data from the literature.[7a] The HPLC analysis of the products with racemic reference compounds[7d] using a chiral column and comparison of specific rotations showed that no isomerization occurred during this reaction (Chiralcel OA column, UV detection at 210 nm, eluent: hexane/2-propanol = 9:1, flow 0.50 mL $min^{-1}$ 20°C, $R_t(S) = 38.3$ min, $R_t(R) = 43.5$ min, 98% e.e.).[17]

The results show that manganese(III) acetate-mediated acetoxylation of enone followed by enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enone (*R*)-**4** and acetoxy enone (*S*)-**3** with high enantiomeric excesses (97–98%) and in good chemical yields.

**Table 1.** Enzymatic hydrolysis of 5-acetoxy-3-methoxycyclopent-2-en-1-one **3**

| No. | Enzyme | Reaction time (h) | Conversion $c$[a] (%) | Acetate | | Alcohol[d] | | $E$[f] |
|---|---|---|---|---|---|---|---|---|
| | | | | E.e.[b] (%) | Yield[c] (%) | E.e.[e] (%) | Yield[c] (%) | |
| 1 | PLE | 22 | 50 | 96 | 37 | 96 | 42 | 196 |
| 2 | Amano PS | 24 | 50 | 97 | 43 | >98 | 45 | 277 |
| 3 | PPL | 36 | – | – | 37 | – | 41 | – |

[a] $c = e.e._s/(e.e._s + e.e._p)$.
[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] Racemization-free acetylation of alcohol (*R*)-**4** was carried out with acetic anhydride/$Cu(OTf)_3$ according to a procedure reported in the literature and (*R*)-**3** was obtained in 84% yield.[14] Likewise, racemization-free hydrolysis of chiral acetoxy enone was carried out with $Sc(OTf)_3$/MeOH–$H_2O$[15] and the reaction furnished (*S*)-**4** in 91% yield. The e.e. of the alcohol was also determined by HPLC via its acetate derivatives.
[e] Determined by HPLC using chiral column (Chiralcel OD column, UV detection at 254 nm, eluent:hexane/2-propanol = 95:5, flow 0.75 mL $min^{-1}$ 20°C, using racemic compounds as references).
[f] Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

The undesired acetoxy enone can be epimerized in good yield and reused. In these conversion reactions, enzymes favor the (*R*)-enantiomers. The reduction of the acetoxy and hydroxy enone followed by acid hydrolysis furnished both enantiomers of 4-hydroxy-cyclopent-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.

## 3. Experimental

### 3.1. General methods

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). Optical rotations were measured with a Bellingham–Stanley P20 polarimeter or Autopol IV automatic polarimeter. Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC–LC–MS equipped with an appropriate optically active column, as described in the corresponding footnotes of Table 1.

**3.1.1. (±)-5-Acetoxy-3-methoxycyclopent-2-en-1-one 3**. A solution of 3-methoxycyclopent-2-en-1-one **2**[9] (2.5 g, 22.3 mmol), $Mn(OAc)_3$ (17.2 g, 66.9 mmol) and cyclohexane or benzene (200 mL) were heated under reflux for 45–54 h. After cooling, the reaction mixture was first filtered then washed with sat. $NaHCO_3$ solution. Dried over $MgSO_4$, concentrated and purified by flash column chromatography (2:1 EtOAc:hexane) to yield 79–83% of racemic 5-acetoxy-3-methoxycyclopent-2-en-1-one (3.1 g) **3**.

### 3.2. General procedure for enzyme-catalyzed hydrolysis

To a stirred solution of (±)-5-acetoxy-3-methoxycyclopent-2-en-1-one **3** (180 mg, 1.1 mmol) in DMSO (2 mL) and phosphate buffer (pH 7.0, 60 mL) enzyme (PLE 200 μL, *Amano* PS and PPL 6 mg) was added in one portion and the reaction mixture was stirred at rt. Conversion was monitored by TLC and LC–MS up to 50%. After filtration, the filtrate was extracted with dichloromethane, dried over $MgSO_4$, concentrated and purified by flash column chromatography (2:1 EtOAc:hexane) to obtain (*S*)-5-acetoxy-3-methoxy-cyclopent-2-en-1-one **3** and (*R*)-5-hydroxy-3-methoxy-cyclopent-2-en-1-one **4** in 37–43% and 42–45% yields, respectively.

(*S*)-**3**: viscous oil, 72.1 mg, $[\alpha]_D^{20}=+29$ ($c=1.6$, $CHCl_3$) [(*R*)-**3** $[\alpha]_D^{20}=-27$ ($c=1.6$, $CHCl_3$)]; $R_t(S)=18.6$ min [$R_t(R)=21.4$ min], 97% e.e.; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.07 (s, 3H), 2.48 (dd, $J=3.2$, 16.8 Hz, 1H), 3.03 (dd, $J=7.3$, 16.8 Hz, 1H), 3.82 (s, 3H), 5.14 (dd, $J=3.2$, 7.3 Hz, 1H), 5.30 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 21.2, 36.2, 59.2, 71.9, 103.4, 170.9, 188.2, 199.9. Anal. calcd for $C_8H_{10}O_4$ (170.16): C, 56.47; H, 5.92; found: C, 56.61; H, 5.88%.

(*R*)-**4**: semisolid, 58.4 mg, $[\alpha]_D^{20}=+17$ ($c=0.5$, $CHCl_3$) [(*S*)-**4** $[\alpha]_D^{20}=-18$ ($c=0.5$, $CHCl_3$)]; $R_t(R)=46.8$ min [$R_t(S)=45.1$ min], >98% e.e.; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.52 (dd, $J=3.2$, 17.7 Hz, 1H), 2.89 (dd, $J=7.1$, 17.7 Hz, 1H), 3.81 (s, 3H), 4.26 (dd, $J=3.2$, 7.1 Hz, 1H), 5.24 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 37.5, 59.1, 71.7, 101.9, 189.0, 206.0. Anal. calcd for $C_6H_8O_3$ (128.13): C, 56.24; H, 6.29; found: C, 56.21; H, 5.98%.

### 3.3. General procedure for reductions

To a suspension of $LiAlH_4$ (33.4 mg, 0.9 mmol) in anhydrous $Et_2O$ (30 mL) was added acetoxy enone (*S*)-**3** (50.3 mg, 0.3 mmol) or hydroxy enone (*S*)-**4** (37.6 mg, 0.3 mmol) at rt over 15 min. The mixture was refluxed for 30 min, cooled to rt and quenched with water and 10% $H_2SO_4$. Organic phase was washed with sat. $NaHCO_3$ solution, brine, and dried over $MgSO_4$. After evaporation of the solvent flash column chromatography (EtOAc) was performed to obtain 4-hydroxy-cyclopent-2-en-1-one **1** in 71–83% yield.

(*R*)-**1**: viscous oil, 24.5 mg, $[\alpha]_D^{20}=+78$ ($c=1.2$, $CHCl_3$), [(*S*)-**1** $[\alpha]_D^{20}=-76$ ($c=1.2$, $CHCl_3$)];[7a] $R_t(S)=38.3$ min [$R_t(R)=43.5$ min, 97–98% e.e.]; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.25 (dd, $J=2.3$, 18.5 Hz, 1H), 2.74 (dd, $J=6.1$, 18.5 Hz, 1H), 3.9 (m, 1H), 5.05 (br.s, 1H), 6.18 (d, $J=5.7$ Hz, 1H), 7.58 (dd, $J=2.3$, 5.7 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 44.2, 70.2, 134.9, 163.9, 207.3

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10. For high yield acetoxylation, manganese(III) acetate must be dried over phosphorus pentaoxide under vacuum prior to use.
11. The source of manganese(III) acetate is important to the yield and the outcome of the reaction. Manganese(III) acetate used in this study was commercial. Alternatively it can be synthesized from manganese(II) nitrate and acetic anhydride.[8b] Since manganese(III) acetate is a hydrate of unspecified composition and forms manganese oxide hydrate with water (see Weinland, R. F.; Fischer, G. *Z. Anorg. Allg. Chem*. **1922**, *120*, 161) the exact content of it is uncertain. Hence, we arbitrarily used an excess of manganese(III) acetate per mole of substrate in our ongoing work. In some cases we also obtained phenyl substituted acetoxy derivatives by using benzene as solvent via formation of phenyl radical, which depends on the reaction conditions and the source of the manganese(III) acetate (see Demir, A. S.; Reis, O.; Ozgul-Karaaslan, E. *J. Chem. Soc., Perkin 1* **2001**, *22*, 3042). This problem is still under investigation.
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17. LAH reduction reaction must be highly stereoselective to give the *S*,*S* (*R*,*R*) diol prior to hydrolysis and elimination of one of the OH groups. This reduction step is still under investigation.