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Chemoenzymatic synthesis of both enantiomers of 4-acetoxy-2-hydroxymethyl-cyclohex-2-en-1-one

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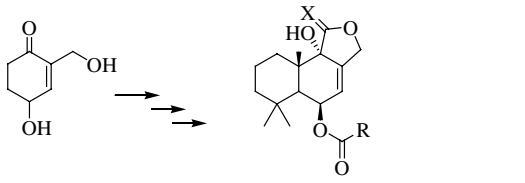
Abstract—A chemoenzymatic synthesis of both enantiomers of the pharmacologically interesting 4-acetoxy-2-hydroxymethyl-cyclohex-2-en-1-one starting from cyclohexane-1,3-dione is described. Cyclohexane-1,3-dione was converted into 4,6,7,8-tetrahydrobenzo[1,3]dioxin-5-one and then manganese(III) acetate-mediated acetoxylation followed by the enzyme-mediated hydrolysis of α-acetoxy enone afforded the acetoxy enone and hydroxy enone with high enantiomeric excesses and in good yields. The reduction of the acetoxy enones furnished both enantiomers of 4-acetoxy-2-hydroxymethyl-cyclohex-2-en-1-one in high enantiomeric excess.

1. Introduction

Chiral γ-hydroxy enones are important structural units in many biologically active natural products and are also important as synthons for the asymmetric synthesis of natural products.[1] 4-Hydroxy-2-hydroxymethyl-cyclohex-2-en-1-one has been employed as a starting material for the syntheses of biologically active compounds such as antibiotics, mono, and sesquiterpenoids[2] (Scheme 1). Kraus et al. used these compounds for the synthesis of synthetic analogues of RES-1149-2, which exhibit endothelin receptor binding activity at the μg/mL level in a human ETA assay.[3]

There is considerable interest in developing efficient methods for the preparation of optically active 4-acetoxy-2-hydroxymethyl-cyclohex-2-en-1-one **1**, which minimize the number of required synthetic steps while maximizing the overall chemical yield and enantiomeric excess of this important intermediate.



x = H, OH, O
R= OH, -CH=CHCH=CHCH$_3$

Scheme 1.

In our ongoing work, we have previously presented an improved procedure for the $Mn(OAc)_3$ mediated α′-acetoxylation of α,β-unsaturated ketones based on the use of acetic acid as a cosolvent.[4a] Excellent results were obtained for a variety of structurally diverse and synthetically important enones under optimized conditions. We additionally reported enzyme- and the fungus-mediated resolution of acyloxy enones for the synthesis of enantiomerically pure α-hydroxy- and α-acetoxy ketones.[4]

The importance of chiral 4-acetoxy-2-hydroxymethyl-cyclohex-2-en-1-one **1**, 6-acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one **4** and 6-hydroxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one **5** led us to explore a chemoenzymatic method for obtaining them in their enantiomerically pure forms. Herein we report an efficient chemoenzymatic route to the synthesis of both enantiomers of **1**, **4**, and **5** starting from cyclohexane-1,3-dione **2**.

2. Results and discussion

The Prins reaction[5] of 1,3-diketones with formaldehyde is a general approach to the 1,3-dioxin vinylogous ester system. According to the Smith procedure,[6]

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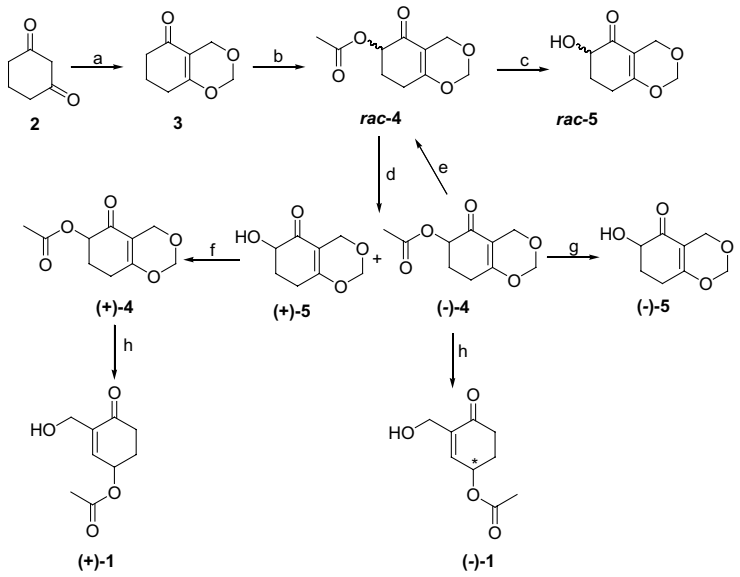

Scheme 2. (a) Paraformaldehyde, $BF_3{\cdot}Et_2O$; (b) $Mn(OAc)_3$, benzene/HOAc; (c) K_2CO_3, MeOH;[4d] (d) enzyme, DMSO, buffer (pH = 7); (e) DBU, hexane, THF;[4d] (f) $Cu(OTf)_2$, Ac_2O;[7] (g) $Sc(OTf)_3$, MeOH, H_2O;[8] (h) $LiBH_4$, ether.

cyclohexane-1,3-dione **2** was converted to the 4,6,7,8-tetrahydro-benzo[1,3]dioxin-5-one **3** using paraformaldehyde in the presence of $BF_3{\cdot}Et_2O$. In an initial reaction (Scheme 2), oxidation of enone **3** with 1.5 equiv of manganese(III) acetate in benzene/acetic acid was performed to obtain the desired 6-acetoxy enone, *rac*-**4**, in a 92% yield after purification by way of column chromatography. Direct synthesis of acyloxy enone *rac*-**4** under mild conditions from enone **3** using manganese(III) acetate is an attractive alternative to the other (multi-step) procedures for α′-oxidation. Lipase-type enzymes are used extensively for the synthesis of enantiomerically pure compounds via the resolution of racemic mixtures. The high stereoselectivity in organic media and their low cost make them very useful catalysts for enantioselective resolution.

Based on our previous work with biocatalyst-mediated reactions,[4] we tested a series of enzymes for screening the enantioselective hydrolysis of acetoxy enone *rac*-**4**. Ester hydrolysis of *rac*-**4** was investigated using several readily available enzymes. All of the enzymes affected the hydrolysis and in these conversion reactions, enzymes favor the (−)-enantiomer of **4** except *Aspergillus*, which showed reverse selectivity. The enzymes PLE and CAL exhibited the highest enantioselectivity. Careful monitoring of the reactions with TLC and HPLC (Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C, using racemic compounds as references) furnished the acetoxy enone (−)-**4** (34–96% ee) and hydroxy enone (+)-**5** (31–95% ee) (Table 1).

In a typical experiment for the enzymatic hydrolysis, racemic acetoxy enone **4** was dissolved in DMSO. The phosphate buffer was added and the mixture was then stirred at room temperature in the presence of an enzyme. The reaction was monitored by TLC analysis and HPLC with a chiral column using acetoxy enone *rac*-**4** and hydroxy enone *rac*-**5** (synthesized from acetoxy enone *rac*-**4** with K_2CO_3/MeOH)[4d] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford acetoxy enone (−)-**4** and hydroxy enone (+)-**5**. The best results were obtained using PLE and CAL. Racemization free acetylation of alcohol (+)-**5** was carried out with acetic anhydride/$Cu(OTf)_2$ according a procedure reported in the literature with (+)-**4** being obtained in a 90% yield.[7] Likewise, racemization free hydrolysis of chiral acetoxy enone was carried out with $Sc(OTf)_3$/MeOH–H_2O[8] with the reaction furnishing (−)-**5** in a 90% yield. Acetoxy enones obtained after bioconversion and acetylation reactions can be epimerized using DBU in hexane/THF[4d] to afford the racemic acetoxy enone **4** in 87–90% yields after purification by column chromatography. Recycling of the ester makes this method quite efficient for the enantioselective synthesis of the desired acetoxy enones. The enantiomers of acetoxy enone **1** with multi-functional groups are quite interesting starting materials for many biologically active compounds.

The reduction and hydrolysis of α′-acetoxy or α′-hydroxy-α,β-unsaturated enone provided access to γ-hydroxy-α,β-unsaturated enone.[4d,e] For the conversion, we tested different reduction reactions. Among them, the reduction reaction of **4** with $LiBH_4$ was found to be the mildest method. $LiBH_4$ reduction of **4** followed by acid treatment furnished the desired 4-acetoxy enone **1** in 83–86% yields after separation of the crude product by column chromatography. Retaining the acetyl-protecting group is advantageous for further modification of the molecule. The HPLC analysis of the products with racemic reference compounds using a chiral column showed that no isomerization occurred during this reaction.

Table 1. Enzymatic hydrolysis of 6-acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one

Enzyme	Reaction time (h)	Conversion *c* (%)[a]	Acetate		Alcohol		*E*[d]
			Ee[b] (%)	Yield[c] (%)	Ee[b] (%)	Yield[c] (%)	
PLE (*pig liver* esterase)	1.5	50	96	43	95	41	153
CAL (*Candida antarctica* lipase)	528	53	90	44	81	43	28
MML (*Mucor miehei* lipase)	96	51	78	39	74	37	15
PCL (*Pseudomonas cepacia* lipase)	5	49	68	41	70	39	11
SL (*Pseudomonas burkholderia cepacia* SL-25)	16	49	60	40	63	40	8
Amano (*Amano PS*)	4	51	57	38	54	38	6
PFL (*Pseudomonas fluorescens* lipase)	8	59	54	41	38	39	4
PPL (*Porcine pancreatic* lipase)	118	49	50	40	52	38	5
HPL (*Hog pancreas* lipase)	336	54	49	37	41	38	4
CCL (*Candida cylindracea* lipase)	312	51	46	38	45	41	4
RAL (*Rhizopus arrhizus* lipase)	336	55	36	43	30	38	3
Aspergillus (*Aspergillus niger*)	8	48	35 (reverse)	41	38	37	3
RNL (*Rhizopus niveus* lipase)	528	52	34	40	31	39	3

[a] $c = ee_s/(ee_s + ee_p)$.
[b] Determined by HPLC using chiral column (Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C, using racemic compounds as references).
[c] Isolated yield after flash column chromatography.
[d] Ref. 9.

3. Conclusion

The results show that the manganese(III) acetate-mediated acetoxylation of the enone followed by the enzyme-mediated hydrolysis of the acetoxy group provides acetoxy enone (−)-**4** and hydroxy enone (+)-**5** with high enantiomeric excesses (95–96%) and in good chemical yields. The undesired acetoxy enone can be epimerized in good yield and reused. The reduction of the acetoxy enone followed by acid treatment furnished both enantiomers of **1** in high enantiomeric excess. This method provides a simple new entry to the synthesis of cyclic 4-acetoxy-2-hydroxymethyl enones, which are important precursors for pharmacologically interesting compounds.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$) and CCl_4 (^{13}C: $\delta = 96.4$) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel 60F_{254} (Merck), and the spots visualized with UV light ($\lambda = 254$ nm). Enantiomeric excesses were determined by HPLC and LC-MS analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column, as described in the footnotes of the Tables. Optical rotations were measured with an Autopol IV automatic polarimeter.

4.1.1. 4,6,7,8-Tetrahydro-5*H*-1,3-benzodioxin-5-one 3.[6] A mixture of 1,3-cyclohexanedione **2** (2.30 g, 20 mmol), paraformaldehyde (3.60 g, 120 mmol), $BF_3{\cdot}Et_2O$ (7.38 mL, 60 mmol) and methylene chloride (150 mL) were stirred at room temperature for 38 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (20 mL) and the aqueous phase extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (1:4 EtOAc/hexane) to yield **3** (2.59 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92–1.98 (m, 2H), 2.25 (t, $J = 6.42$ Hz, 2H), 2.35 (t, $J = 5.91$ Hz, 2H), 4.34 (bs, 2H), 5.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 170.1, 112.0, 91.6, 62.9, 36.6, 27.8, 20.9.

4.1.2. *rac*-6-Acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one *rac*-4. A solution of 1,3-dioxin vinylogous ester **3** (1.20 g, 7.8 mmol) and $Mn(OAc)_3$ (2.84 g, 10.6 mmol) in 100 mL benzene/AcOH (10:1) was stirred under reflux (Dean-Stark apparatus) during which the

dark brown color of $Mn(OAc)_3$ disappeared; this was also monitored by GC–MS and TLC. The reaction mixture was diluted with ether and washed with brine. The resulting organic phase was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (1:5 EtOAc/hexane) to yield **4** as colorless solid (1.52 g, 92%), mp 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04–2.10 (m, 1H, CH_2), 2.07 (s, 3H, CH_3), 2.12–2.17 (m, 1H, CH_2), 2.42–2.48 (m, 1H, CH_2), 2.56–2.61 (m, 1H, CH_2), 4.24 (dd, J = 14.55, 2.30 Hz, 1H, CH_2), 4.39 (dt, J = 12.69, 1.91 Hz, 1H, CH_2), 4.98 (d, J = 5.52 Hz, 1H, CH_2), 5.14 (d, J = 5.49 Hz, 1H, CH_2), 5.19 (dd, J = 12.62, 5.24 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 170.1, 169.1, 110.9, 91.6, 72.1, 62.9, 26.9, 26.7, 21.1. Anal. Calcd for $C_{10}H_{12}O_5$ (212.2): C, 56.60; H, 5.70. Found: C, 56.45; H, 5.66.

4.2. General procedure for the lipase-catalyzed hydrolysis of 6-acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one

To a stirred solution of *rac*-6-acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one *rac*-**4** (300 mg, 1.76 mmol) in DMSO (2 mL) and phosphate buffer (pH 7.0, 75 mL), enzyme (PLE 300 μL) was added in one portion and the reaction mixture stirred at rt. Conversion was monitored by TLC and when 50% conversion was attained, the reaction was terminated by the addition of excess organic solvent (chloroform). After filtration, the filtrate was extracted with dichloromethane, dried over $MgSO_4$, concentrated, and the unreacted acetate and product separated by column chromatography (2:1 EtOAc/hexane) to obtain (−)-6-acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one (−)-**4** and (+)-6-hydroxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one (+)-**5**, respectively.

4.2.1. (−)-6-Acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one (−)-4. Colorless solid (129 mg, 43%), mp 67–68 °C $[\alpha]_D^{25} = -163.6$ (c 1, CH_3OH). HPLC: Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C retention time: 30.3 min.

4.2.2. (+)-6-Acetoxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one (+)-4. $[\alpha]_D^{25} = +165.2$ (c 1, CH_3OH).

4.2.3. (+)-6-Hydroxy-4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-one (+)-5.[3] Colorless solid (122.6 mg, 41%), mp 114–115 °C [lit.[3] no mp]. $[\alpha]_D^{25} = +219.2$ (c 0.1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) 1.80 (ddd, J = 25.35, 12.7, 5.41 Hz, 1H, CH_2), 2.29–2.34 (m, 1H, CH_2), 2.39–2.45 (m, 1H, CH_2), 2.50–2.70 (m, 1H, CH_2), 3.58 (bs, 1H, OH), 3.95–4.05 (m, 1H, CH), 4.28 (dd, J = 14.5, 2.12 Hz, 1H, CH_2), 4.48 (d, J = 14.51 Hz, 1H, CH_2), 4.99 (d, J = 5.5 Hz, 1H, CH_2), 5.17 (d, J = 5.49 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 170.6, 109.4, 91.9, 71.2, 62.7, 29.3, 27.1.

HPLC: Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C retention time: 19.35 min.

4.2.4. (−)-4-Acetoxy-2-hydroxymethyl-2-cyclohex-2-en-1-one (−)-1. To a stirred solution of (−)-**4** (41 mg, 0.24 mmol) in 5 mL of dry ether, cooled to 0 °C was added 0.36 mmol of $LiBH_4$. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, cooled back to 0 °C and then quenched by the addition of saturated aqueous Na_2SO_4 (0.5 mL). The insoluble salts were removed by filtration and the filtrate concentrated in vacuo. The resultant oil was then dissolved in 2 mL of THF and 0.2 mL of 2 M HCl added. After 15 min, the reaction was neutralized with aqueous K_2CO_3, diluted with ether, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (2:1 EtOAc/hexane) to yield (−)-**1** as a colorless oil (38 mg, 86%). $[\alpha]_D^{25} = -71.4$ (c 0.3, CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (bs, 1H, OH), 1.97–2.06 (m, 1H), 2.04 (s, 3H), 2.27–2.31 (m, 1H), 2.35–2.44 (m, 1H), 2.58 (dt, J = 16.95, 5.26 Hz, 1H), 4.20 (s, 2H), 5.5 (m, 1H), 6.71 (d, J = 1.25 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 170.2, 143.0, 139.9, 68.2, 61.5, 35.6, 29.1, 21.3. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.46; H, 6.61. HPLC: Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C retention time: 43.4 min.

4.2.5. (+)-4-Acetoxy-2-hydroxymethyl-2-cyclohex-2-en-1-one (+)-1. 37 mg (83%), $[\alpha]_D^{25} = +73.1$ (c 0.3, CH_3Cl). HPLC: Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.80 mL min^{-1} 20 °C retention time: 53.1 min.

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