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A new and efficient chemoenzymatic route to both enantiomers of α′-acetoxy-α-methyl and γ-hydroxy-α-methyl cyclic enones

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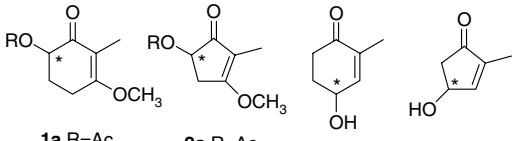
Abstract—A chemoenzymatic synthesis of both enantiomers of the pharmacologically interesting α′-acetoxy-α-methyl and γ-hydroxy-α-methyl cyclic enones starting from α-methyl-β-methoxy cyclic enones is reported. Manganese(III) acetate-mediated acetoxylation followed by the enzyme-mediated hydrolysis of α′-acetoxy enone provides acetoxy enones **1a** and **2a** and hydroxy enones **1b** and **2b** with high enantiomeric excesses in good yields. The reduction of the acetoxy and hydroxy enones furnished both enantiomers of γ-hydroxy-α-methyl cyclic enones **3** and **4** in a high enantiomeric excess.

1. Introduction

Chiral cyclic polyoxo-ketones **1**–**4** are important structural units in many biologically active compounds and are important synthons for the asymmetric synthesis of natural products.[1] It is therefore of considerable interest to develop efficient methods for the preparation of these compounds in enantiomerically pure forms.



1a R=Ac **1b** R=H **2a** R=Ac **2b** R=H **3** **4**

Several preparations of racemic **1**, **2**[2], **3**,[3] and **4**[4] have been published, but few examples have reported the asymmetric synthesis of **3** and **4**. The synthesis of (*R*)-**3** has been described by Schultz et al.[5] Fragmentation reactions of 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones furnished (*R*)-**3** in a 72% yield together with the corresponding butenolide carboxylic acid. (*S*)-**4** was synthesized via enzymatic kinetic resolution of rac-**4** and converted to (−)-*fastigilin* C. A PPL mediated resolution of *rac*-**4** with β,β,β-trifluoroethyl butyrate in ether furnished the (*S*)-alcohol (43%, 68% ee) together with the (*R*)-butyrate. (*R*)-Butyrate, isolated by column chromatography, was cleaved to the (*R*)-alcohol (78%, 46% ee) and the stereocenter inverted via a Mitsunobu protocol, furnishing an additional quantity of the (*S*)-alcohol (52%, 46% ee). The combined (*S*)-**4** (60% ee) batches were exposed again to β,β,β-trifluoroethyl butyrate and PPL in ether to provide (*S*)-**4** in a 52% isolated yield and >98% ee.[6]

In our ongoing investigations, we have published several papers concerning 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.[7] Due to the multi-functional nature of chiral α′-hydroxy-α-methyl, α′-acetoxy-α-methyl, and γ-hydroxy-α-methyl cyclic enones **1**–**4**, they can take part in several stereoselective transformations, which led us to explore a chemoenzymatic method for obtaining them in their enantiomerically pure forms. We describe herein an efficient chemoenzymatic route to the three-step synthesis of both enantiomers of **1**–**4** starting from 3-methoxy-2-methyl-cyclic enones **5** and **6**, which are a representative example for the simple enantioselective synthesis of cyclic 2-substituted 4-hydroxy enones.

2. Result and discussion

Commercially available 1,3-diones 2-methylcyclopentan-1,3-dione and 2-methylcyclohexan-1,3-dione were

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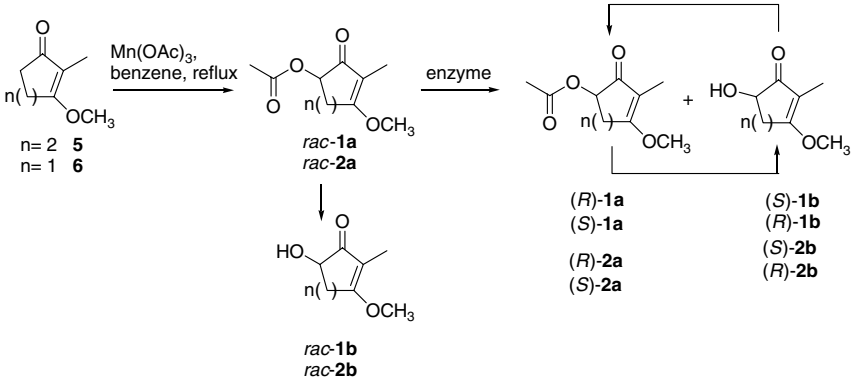
converted to the 3-methoxy-2-methyl cyclic enones **5** and **6** using a procedure previously reported in literature.[8] As an initial reaction (Scheme 1), oxidation of the enone **5** and **6** with four equivalents of manganese(III) acetate in benzene was performed to obtain the desired α′-acetoxy enones, *rac*-**1** and **2**, in 85-88% yield after purification by column chromatography. Direct synthesis of acyloxy enones *rac*-**1** and **2** under mild conditions from enones **5** and **6** 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.[9]

Based on the preliminary information available to us from our previous work with biocatalyst-mediated reactions,[7c,d] we tested a series of enzymes for screening the enantioselective hydrolysis of acetoxy enone *rac*-**1a**. As shown in Table 1, seven enzymes: PLE (*Pig Liver* esterase), *Amano* PS, CCL (*Candida Cylindracea* lipase), PPL (*Porcine Pancreatic* lipase), Lipase TL (*Pseudomonas Stutzeri* PL-836), Lipase SL (*Pseudomonas* (*Burkholderia*) *cepacia* SL-25), and Lipase QLM (*Burkholderia Graduloi*) showed activity via the hydrolysis of *rac*-**1a**. For the kinetic resolution step, the following conditions provided the optimal results.

In a typical experiment for enzymatic hydrolysis, the racemic 4-methoxy-3-methyl-2-oxocyclohex-3-en-1-yl acetate, *rac*-**1a**, was dissolved in DMSO, a phosphate buffer (pH 7.0) then added and the mixture stirred at room temperature in the presence of the enzyme. The reaction was monitored by TLC analysis and LC–MS with a chiral column using *rac*-**1a**, and *rac*-6-hydroxy-3-methoxy-2-methylcyclohex-2-en-1-one, *rac*-**1b**, (synthesized from *rac*-**1a** with K_2CO_3/MeOH)[7c,d] as references. When an approximately 50% conversion was attained, the crude product was separated by flash column chromatography to provide (*S*)-4-methoxy-3-methyl-2-oxocyclohex-3-en-1-yl acetate, (*S*)-**1a**, and (*R*)-6-hydroxy-3-methoxy-2-methylcyclohex-2-en-1-one, (*R*)-**1b**. All enzymes affected the hydrolysis and preferentially recognized the (*R*)-enantiomer of *rac*-**1a**. Careful monitoring of the reactions with TLC and LC–MS provided the acetoxy enone (*S*)-**1a** (50 to >98% ee, 41–51% yields) and hydroxy enone (*R*)-**1b** (55 to >96% ee, 37–48% yields). PLE, *Amano* PS and PPL exhibited high enantioselectivity for the remaining acetoxy enone (>98% ee) while PLE, PPL, TL, SL exhibited high enantioselectivity for the hydroxyl enone (94–96% ee)



Scheme 1.

Table 1. Enzymatic hydrolysis of 4-methoxy-3-methyl-2-oxocyclohex-3-en-1-yl acetate *rac*-**1a**

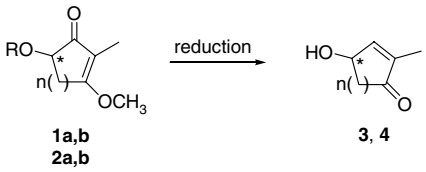
No	Enzyme	Reaction time (h)	Conversion c^a (%)	Acetate		Alcohol		E^d
				Ee[b] (%)	Yield[c] (%)	Ee[b] (%)	Yield[c] (%)	
1	PLE	24	51	>98	45	96	47	>200
2	*Amano PS*	22	47	>98	41	88	45	>200
3	CCL	24	58	60	50	55	43	5
4	PPL	23	51	>98	49	95	37	180
5	TL[e]	8 d	35	50	49	94	41	53
6	SL[e]	52	48	86	47	95	38	108
7	QLM[e]	12	48	77	51	82	48	23

[a] $c = ee_s/(ee_s + ee_p)$.
[b] Determined by HPLC using the chiral column (Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 75:25, flow 0.80 mL min^{-1} 20 °C, using racemic compounds as references; R_f: for (*S*)-**1a**: 20 min; (*R*)-**1a**: 27 min; R_f: for (*R*)-**1b**: 10 min; (*S*)-**1b**: 8 min).
[c] Isolated yield after flash column chromatography.
[d] See Ref. 13. *E* values are calculated using the program 'Selectivity' by K. Faber and H. Hoenig, http://www.cis.TUGraz.at/orgc/.
[e] MEITO SANGYO Co., Ltd., Tokyo, Japan.

(Table 1). Among the organic solvents used (toluene, xylene, THF, dioxane, acetonitrile, benzene, and ether) DMSO provided the optimal results.

Under the above mentioned conditions, the enantioselective hydrolysis of 4-methoxy-3-methyl-2-oxocyclopent-3-en-1-yl acetate *rac*-**2a** was investigated with four readily available enzymes: PLE (*Pig Liver* esterase), *Amano* PS, CCL (*Candida Cylindracea* lipase) and PPL (*Porcine Pancreatic* lipase). Careful monitoring of the reactions with TLC and LC–MS provided the acetoxy enone (*R*)-**2a** (28–98% ee, 41–54% yields) and hydroxy enone (*S*)-**2b** (32–95% ee, 37–47% yields). PLE and *Amano* PS exhibited high enantioselectivity for both acetoxy enone (97–98% ee), and hydroxyl enone (93–95% ee) (Table 1). The enzymes PLE (*Pig Liver* esterase), *Amano* PS, and CCL (*Candida Cylindracea* lipase) preferentially recognized the (*S*)-enantiomer of *rac*-**2a**, while PPL preferentially recognized the (*R*)-enantiomer of *rac*-**2a** (Table 2, Scheme 1).

The absolute configuration of products **1** and **2** was based on the absolute configuration of the known final products **3**[5] and **4**.[6] As we reported earlier for related systems, racemization free interconversion of acetate to alcohol and vice versa gives additional flexibility to this method.[7c,d,10,11] Since the reduction of α′-acetoxy or α′-hydroxy-α,β-unsaturated enone **1** and **2** provide access to γ-hydroxy-α,β-unsaturated enone,[7c,d] the reaction of **1** and **2** with $LiAlH_4$ followed by acid catalyzed hydrolysis and elimination furnished the desired products **3** and **4** in 79–81% yields after separation of the crude product by column chromatography. The absolute configuration of the product was assessed by comparison of its specific rotation and HPLC data with data from the literature.[5,6] The chiroptical comparison and HPLC analysis of the products **3** and **4** with racemic reference compounds using a chiral column showed that no isomerization occurred during this reaction. For the high yield formation of **3** and **4** we suggest that either the reduction works with high selectivity or acid or base catalyzed isomerization at the α-position occurs during the elimination. Until now it has not been possible to isolate the reduction products before elimination; therefore we cannot give an exact mechanism for this step. The reason for this behavior is still under investigation (Scheme 2).



Scheme 2.

3. Conclusion

The results show that manganese(III) acetate-mediated acetoxylation of an enone followed by enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enones **1b** and **2b** and acetoxy enone **1a** and **1b** with high enantiomeric excesses (95 to >98%) in good chemical yields. In these conversion reactions, the enzymes favor the (*R*)-enantiomer with six-member ring compound **1a** while most of the enzymes shows reverse selectivity with five-member ring compound **2a**. The reduction of the acetoxy and hydroxy enone followed by acid hydrolysis provided both enantiomers of 4-hydroxy-2-methyl cyclohex-2-en-1-one **3** and 4-hydroxy-2-methyl cyclopent-2-en-1-one **4** in a high enantiomeric excess. This method provides a simple new entry to the synthesis of cyclic 4-hydroxy 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. 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) GCLCMS equipped with an appropriate optically active column.

4.2. General procedures

4.2.1. General procedure for $Mn(OAc)_3$ oxidation. A solution of **5** and **6** (22.3 mmol), $Mn(OAc)_3$ (17.2 g,

Table 2. Enzymatic hydrolysis of 4-methoxy-3-methyl-2-oxocyclopent-3-en-1-yl acetate (*rac*-**1b**)

No	Enzyme	Reaction time (h)	Conversion c[a] (%)	Acetate		Alcohol		E[d]
				Ee[b] (%)	Yield[c] (%)	Ee[b] (%)	Yield[c] (%)	
1	PLE	16	51	98	45	95	47	180
2	*Amano PS*	22	51	97	41	93	45	115
3	CCL	28 d	44	68	51	87	43	29
4	PPL	23 d	53	28	54	32	37	3

[a] $c = ee_s/(ee_s + ee_p)$.
[b] Determined by HPLC using chiral column (Chiralpak OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 75:25, flow 0.80 mL min^{-1} 20 °C, using racemic compounds as references; R_f: for (*S*)-**2a**: 50 min; (*R*)-**2a**: 22 min; R_f: for (*R*)-**2b**: 15 min; (*S*)-**2b**: 10 min).
[c] Isolated yield after flash column chromatography.
[d] See Ref. 13. *E* values are calculated using the program 'Selectivity' by K. Faber and H. Hoenig, http://www.cis.TUGraz.at/orgc/.

66.9 mmol) and benzene (200 mL) were heated under reflux for 30–54 h. After cooling, the reaction mixture was first filtered and then washed with satd $NaHCO_3$ solution. The mixture was then dried over $MgSO_4$, concentrated and purified by flash column chromatography (2:1 EtOAc/hexane) to yield *rac*-**1a** and *rac*-**2a**.

4.2.2. General procedure for the lipase-catalyzed asymmetric hydrolysis of *rac*-1a and *rac*-2a. Lipase (200–300 mg) was dissolved in a potassium phosphate buffer (20 mM, pH 7, 30 mL) and added to a solution of the pure substrate **1a** and **2a** (1 mmol) in DMSO (3 mL) and the reaction mixture left to stir at rt. The reaction was monitored by TLC and HPLC and when maximum conversion was reached, the reaction was terminated by filtration. The unreacted acetate and product were separated by flash chromatography over silica (*n*-hexane/ethyl acetate, 4:1).

4.2.2.1. (*S*)-6-Acetoxy-3-methoxy-2-methyl-2-cyclohexen-1-one, (*S*)-1a.[2d] Yellow semi-solid. (97 mg); $[\alpha]_D^{20} = -87.9$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): $\nu = 1735$, 1640, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H, CH_3), 1.99 (ddd, $J = 24.0$, 12.5, 5.7 Hz, 1H, H-5), 2.09 (s, 3H, $COCH_3$), 2.19 (m, 1H, H-5), 2.60 (m, 1H, H-4), 2.70 (m, 1H, H-4), 3.77 (s, 3H, OCH_3), 5.15 (dd, $J = 12.9$, 5.1 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 21.2, 23.9, 26.7, 55.5, 72.3, 114.2, 170.2, 170.3, 192.5.

4.2.2.2. (*R*)-6-Hydroxy-3-methoxy-2-methyl-2-cyclohexen-1-one, (*R*)-1b. Colorless semi-solid. (73 mg). $[\alpha]_D^{20} = +167.3$ (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): $\nu = 3250$, 1650, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 3H, CH_3), 1.69 (ddd, $J = 5.4$, 12.4, 25.5 Hz, 1H, H-5), 2.34 (m, 1H, H-5), 2.54 (m, 1H, H-4), 2.68 (m, 1H, H-4), 3.79 (s, 3H, OCH_3), 3.88 (dd, $J = 5.4$, 13.3 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 24.0, 29.4, 55.4, 71.0, 112.4, 171.5, 198.8. Anal. Calcd for $C_8H_{12}O_3$ (156.18): C, 61.52; H, 7.74. Found: C, 61.21; H, 7.98.

4.2.2.3. (*R*)-4-Methoxy-3-methyl-2-oxocyclopent-3-en-1-yl acetate, (*R*)-2a.[2d,e] Yellow oil (83 mg). $[\alpha]_D^{20} = +32.1$ (*c* 0.01, $CHCl_3$); IR ($CHCl_3$): $\nu = 1750$, 1710, 1630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3H, CH_3), 2.05 (s, 3H, $COCH_3$), 2.43 (dd, $J = 17.4$, 1.5 Hz, 1H, CH_2), 3.14 (ddd, $J = 17.4$, 6.8, 1.5 Hz, 1H, CH_2), 3.9 (s, 3H, OCH_3), 5.03 (dd, $J = 6.8$, 2.5 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCI_3$) δ 197.5, 179.9, 169.2, 114.4, 69.9, 55.7, 31.9, 19.6, 4.9.

4.2.2.4. (*S*)-5-Hydroxy-3-methoxy-2-methylcyclopent-2-en-1-one, (*S*)-2b.[12] Colorless solid (47 mg). Mp 155–157 (lit.[12] 158–161 °C). $[\alpha]_D^{20} = +78.8$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): $\nu = 3450$, 1710, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (t, 3H, $J = 1.9$, CH_3), 2.48 (dt, $J = 17.0$, 1.9 Hz, 1H, CH_2), 2.96 (ddd, $J = 17.0$, 6.5, 1.9 Hz, 1H, CH_2), 3.33 (br s, OH), 3.92 (s, 3H, OCH_3), 4.17 (d, $J = 6.5$ Hz,1H, CH); ^{13}C NMR (100 MHz, $CDCI_3$) δ 205.0, 182.2, 115.2, 70.9, 57.1, 34.3, 6.2.

4.2.3. General procedure for reductions. To a suspension of $LiAlH_4$ (66.8 mg, 1.8 mmol) in anhydrous Et_2O (50 mL) was added acetoxy enone (1 mmol) or hydroxy enone (1 mmol) at rt over 15 min. The mixture was refluxed for 30–50 min, cooled to rt and quenched with water and 10% H_2SO_4. The organic phase was washed with satd $NaHCO_3$ solution and brine and then dried over $MgSO_4$. After evaporation of the solvent flash column chromatography (EtOAc) was performed to obtain 4-hydroxy cyclic enones **3** and **4** in 79–81% yield.

4.2.3.1. (*R*)-4-Hydroxy-2-methyl-2-cyclohexen-1-one, (*R*)-3.[3,5] Light yellow semi-solid. (100 mg, 79%); $[\alpha]_D^{20} = +46.7$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): $\nu = 3300$, 1715, 1635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.73 (t, $J = 1.3$ Hz, 3H, Me-2), 1.88 (m, 1H, H-5), 2.27 (m, 2H, H-5 + H-6), 2.53 (m, 1H, H-6), 4.44 (m, 1H, H-4), 6.60 (m, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 32.7, 35.3, 66.4, 135.6, 147.7, 199.1.

4.2.3.2. (*S*)-4-Hydroxy-2-methylcyclopent-2-en-1-one, (*S*)-4.[6] Yellow oil (91 mg). $[\alpha]_D^{20} = -33.5$ (*c* 1.1, $CHCl_3$) {lit.[6] $[\alpha]_D^{20} = -30.0$ (*c* 1.2, $CHCI_3$)}; IR ($CHCI_3$): $\nu = 3400$, 1710, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H, CH_3), 2.07 (br s, 1H, OH), 2.2 (dd, $J = 18.5$, 1.8 Hz, 1H, CH_2), 2.71 (dd, $J = 18.5$, 6.07 Hz, 1H, CH_2), 4.85 (m, 1H, CHOH), 7.09 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCI_3$) δ 206.2, 156.7, 144.0, 68.8, 44.8, 10.3.

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