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Chemoenzymatic synthesis of both enantiomers of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one

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Abstract—4-Oxo-3,4-dihydro-2-chromen-3-yl acetate is synthesized using manganese(III)acetate starting from 2,3-dihydro-4*H*-chromen-4-one. K_2CO_3 mediated hydrolysis of 4-oxo-3,4-dihdro-2-chromen-3-yl acetate furnished 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one in high yield.The enantioselective hydrolysis of (±)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate in various organic solvent-phosphate buffer (pH7) systems and enantioselective transesterification of (±)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one in organic solvents was investigated by screening a range of lipases. The lipase Amano PS, PPL, PLE and CCL-catalyzed asymmetric ester hydrolysis and transesterification afforded the enantiomers of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one and 4-oxo-3,4-dihydro-2-chromen-3-yl acetate with high enantiomeric excess (up to 97% ee) and in good yields.

1. Introduction

3-Hydroxy-2,3-dihydro-4*H*-chromen-4-one **1** is an important precursor for the synthesis of *cis*-4-aminochroman-3-ol **2**.[1] This and related amino alcohols have been used successfully in a 'conformational toolbox' of oxazoline ligands,[2] e.g. in the synthesis of the HIV protease inhibitors[3] and benzopyrane type potassium-channel activators.[4] Hansen et al.[5] synthesized *cis*-4-aminochroman-3-ol **2** starting from homochiral 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one **1**. It was not possible to obtain *cis*-4-aminochroman-3-ol **2** starting from chromene via asymmetric epoxidation followed by a Ritter reaction. There are several methods in the literature for the synthesis of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-ones,[6] but there are few examples of the enantioselective synthesis of these compounds. Hansen et al.[5] applied the catalytic asymmetric synthesis of α-aryloxy alcohols methodology from Jacobsen et al.[7] and synthesized 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one in 94% ee in four steps starting from methyl glycidate and phenol on a large scale.

The kinetic resolution of methyl glycidate via asymmetric ring opening (ARO) with phenol, catalyzed by a chiral (salen)Co(III) complex, gave an α-hydroxy ester in high chemical and enantiomeric excess. Cyclization of the corresponding hydroxy acid furnished homochiral 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one (**1**). The stereochemistry is established by using a homochiral (salen)Co(III) complex.

We recently developed the synthesis of (1*S*,2*R*)-1-amino-2-indanol, a key component of an HIV protease inhibitor.[8] The synthesis was accomplished in four steps starting from indanone efficiently and with high levels of diastereo- and enantioselectivity. Indanone was converted into 2-acetoxy-1-indanone involving manganese(III)acetate oxidation. The 2-acetoxy ketone is hydrolyzed to 2-hydroxy-1-indanone enantioselectively using *Rhizopus oryzae*. Selective reduction of the 2-hydroxy oxime derivative, derived from the 2-hydroxy ketone, gives the amino alcohol up to 98% diastereo- and enantioselectivity (Scheme 1). Therein we wish to report a simple chemoenzymatic access to the both enantiomers of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one **1** starting form 2,3-dihydro-4*H*-chromen-4-one **3a** via manganese(III)acetate mediated acetoxylation followed by enzymatic kinetic resolution. As far as we know, no previous enzymatic kinetic resolution reaction is carried out on these compounds.

2. Results and discussion

In our ongoing work, we have published several papers on the $Mn(OAc)_3$-mediated direct acetoxylation and

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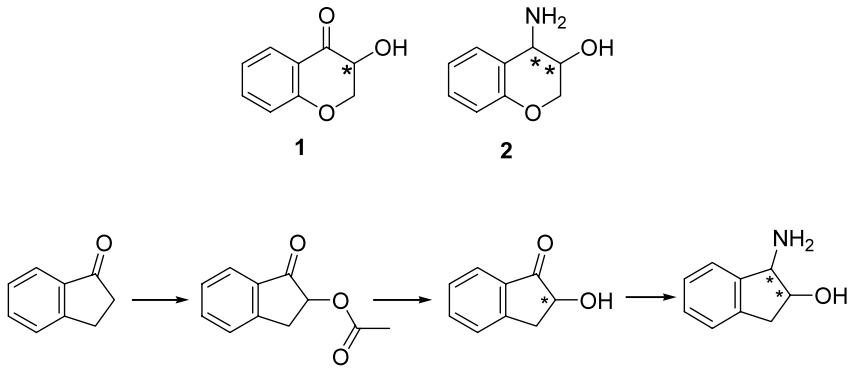


Scheme 1.

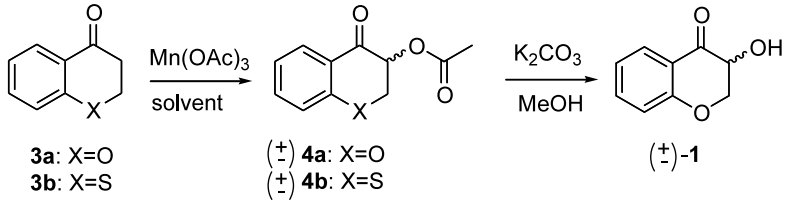
acyloxylation (carried out via metathesis of acetic acid with various carboxylic acids) of enones and aromatic ketones followed by the enzyme- and fungus-mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones.[9] The great importance of homochiral 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one **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 two-step synthesis of both enantiomers of **1** starting from 2,3-dihydro-4*H*-chromen-4-one **3a** (Scheme 2).

As an initial reaction (Scheme 2), oxidation of commercially available 2,3-dihydro-4*H*-chromen-4-one **3a** with 4 equiv. of manganese(III)acetate in cyclohexane or benzene was performed to obtain the desired 4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-**4a**, in 82–90% yield after purification by column chromatography. Manganese(III)acetate mediated oxidation of 2,3-dihydro-4*H*-thiochromen-4-one **3b** furnished 4-oxo-3,4-dihydro-2-thiochromen-3-yl acetate **4b** in 89% yield after purification. Direct synthesis of acyloxy enone (±)-**4** under mild conditions from **3a** and **3b** using manganese(III) acetate is an attractive alternative to the other (multistep) procedures for α′-oxidation.[10]

Lipase type enzymes are used extensively for the synthesis of enantiomerically pure compounds via resolution of racemic mixtures. The high stereoselectivity in aqueous-organic media and their low cost make them very useful catalysts for enantioselective resolutions.[11] On the basis of the preliminary information available to us from our previous work on biocatalyst-mediated reactions,[9] we tried a series of enzymes for screening the enantioselective hydrolysis of 4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-**4a**, and transesterification of (±)-**1**.

Ester hydrolysis of (±)-**4a** was investigated using four readily available enzymes: PLE (pig liver esterase), Amano PS, CCL (*Candida cylindracea* lipase), and PPL (porcine pancreatic lipase). In a typical experiment, for enzymatic hydrolysis, the racemic 4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-**4a**, was dissolved in DMSO, then phosphate buffer (pH 7.0;) (1:10) 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 (±)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-**4a**, and (±)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one, (±)-**1**, (synthesized from (±)-**4a** with K_2CO_3/MeOH)[9] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford (−)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (−)-**4a**, and (+)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one, (+)-**1**. All enzymes achieved the hydrolysis. Best results were obtained using Amano PS and PPL. Careful monitoring of the reactions with TLC and LC-MS furnished the (−)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (−)-**4a**, (25–69% ee) and (+)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one, (+)-**1,** (32-67% ee) (Table 1, Scheme 3).

In view of these promising results, we decided to study the effect of the reaction parameters on the enantioselectivity of the hydrolysis of 4-oxo-3,4-dihydro-2-

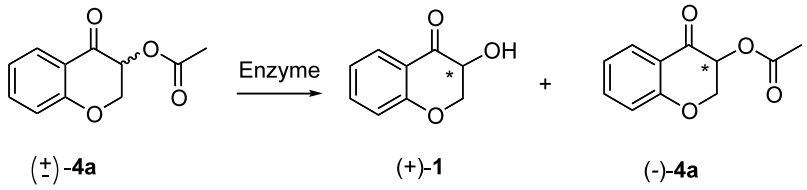


Scheme 2.

Table 1. Enzyme catalyzed hydrolysis of (±)-**4a**

Enzyme	Time (min)	Acetate (−)-**4a**		Hydroxy (+)-**1**		*c*	*E*[b],[12]
		ee[a] (%)	Yield(%)	ee[a] (%)	Yield (%)		
Amano PS	35	69	38	67	44	51	10
PPL	240	57	39	55	41	51	6
CCL	30	29	40	51	38	36	4
PLE	35	25	34	32	36	44	2

[a] Determined with HPLC (Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 9:1, flow 0.8 ml min^{-1}; R_f: for (−)-**4a**:12.1 min; (+)-**4a**: 13.2 min.; R_f for (+)-**1**: 21.4 min; (−)-**1**: 23.4 min.
[b] *E* values are calculated using the program 'Selectivity' by K. Faber and H. Hoenig, http://www.cis.TUGraz.at/orgc/.



Scheme 3.

chromen-3-yl acetate ((±)-**4a**). Taking into account that the temperature can have an effect on the enantioselectivity, we lowered it to 5°C in all the enzyme reactions. At this temperature the reaction rate decreased considerably but we did not observe an improvement in enantioselectivity. Next, we studied the influence of solvents at room temperature. A second screening was performed in various organic solvent-phosphate buffer (pH 7) systems using two lipases that exhibited relatively high *E* values. Table 2 summarizes the results of the experiments performed by Amano *PS* in various organic solvents (organic solvent: phosphate buffer 1:10).The enantioselectivity in the hydrolysis of (±)-**4a** was strongly affected by the nature of the solvent. It is apparent that aromatic solvents such as; benzene, toluene and xylene induced high selectivity in the hyrolysis of acetate. In all solvents tested, the enzymes recognized preferentially the (+)-enantiomer of (±)-**4a**.The best result, $E = 164$, was obtained when Amano PS (*Pseudomonas* sp.) lipase was used in toluene–phosphate buffer (pH 7).

Considering these results, the same solvent systems were tried on the PPL catalyzed hydrolysis of (±)-**4a** (Table 3). However, this time, xylene was the only solvent which gave high selectivity with fast reacting enantiomer. The ee of the remaining unreacted ester was lower than the alcohol.

In all solvents tested, PPL also recognized preferentially the (+)-enantiomer of (±)-**4a**.The best result, $E > 200$, was obtained when PPL was used in xylene–phosphate buffer (pH 7).

We next examined transesterification of (±)-**1** with different organic solvents. As shown in Scheme 4 asymmetric transesterification of (±)-**1** was carried out with Lipase Amano PS, PPL, PLE and CCL using isopropenyl acetate in benzene, toluene, and xylene at a molar ratio of isopropenyl acetate to (±)-**1** of 2:1 (Scheme 4).

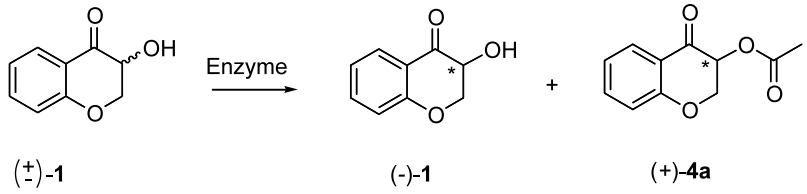
In the transesterification of (±)-**1** only PPL displayed high enantioselectivity towards **1.** In regard to the ee of the remaining substrate (−)-**1** (88%) and that of the product (+)-**4a** (94%) as well as the yield of the reaction (39–43%) PPL was the only promising lipase employed in the transesterification of (±)-**1** in toluene ($c = 48$; $E = 94$), other enzymes showed very low to moderate

Table 2. Amano PS-catalyzed hydrolysis of (±)-**4a**

Solvent	Time(min)	Acetate (−)-**4a**		Hydroxy (+)-**1**		*c*	*E*
		ee (%)	Yield (%)	ee (%)	Yield (%)		
DMSO	35	29	38	57	35	34	5
Ether	60	34	41	37	34	48	3
Toluene	60	97	36	95	44	51	164
Dioxane	75	17	33	49	35	26	3
THF	40	32	40	73	32	30	9
Acetonitrile	75	21	36	36	39	37	3
Benzene	35	67	43	60	38	53	8
Xylene	90	75	26	67	41	53	11

Table 3. PPL-catalyzed hydrolysis of (±)-**4a**

Solvent	Time(h)	Acetate (−)-**4a**		Hydroxy (+)-**1**		*c*	*E*
		ee (%)	Yield (%)	ee (%)	Yield (%)		
DMSO	4	27	39	45	39	38	3
Ether	6	25	45	35	34	42	3
Toluene	24	65	44	75	37	46	13
Dioxane	20	7	35	40	30	15	3
THF	24	29	38	65	43	31	6
Xylene	24	94	47	97	41	49	>200
Benzene	24	25	45	30	42	45	2
Acetonitrile	24	20	35	65	38	24	6



Scheme 4.

enantioselectivities and yields**.** The enzyme preferentially transformed the (+)-enantiomer. The results show that the enzymatic hydrolysis reaction of the acetate (±)-**4a** works better than the transesterification experiments with respect to the ee and yields for the synthesis of (+)- and (−)-**1**. Compared to the enzymatic hydrolysis of acetate in aqueous–organic medium described above, the transesterification experiments in the non-aqueous medium proceeded slowly.

Enzyme catalyzed ester hydrolysis was applied to the resolution of 4-oxo-3,4-dihydro-2-thiochromen-3-yl acetate (±)-**4b** as described above for (±)-**4a** but no reaction was observed. The inhibition of the enzyme by 4-oxo-3,4-dihydro-2-thiochromen-3-yl acetate could be the reason for these results.

Esters (−)-and (+)-**4a** were hydrolyzed using $Sc(OTf)_3$ (20 mol%)[13] to give (−)- and (+)-**1** without any loss of enantiomeric excess.

3. Conclusion

In summary, we have described here, the first efficient synthesis of both enantiomers of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one, and 4-oxo-3,4-dihydro-2-chromen-3-yl acetate via enzymatic kinetic resolution. Manganese(III)acetate mediated acetoxylation of 2,3-dihydro-4*H*-chromen-4-one furnished (±)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate in high yield. Hydrolysis of 4-oxo-3,4-dihydro-2-chromen-3-yl acetate with K_2CO_3 in methanol afforded (±)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one. The enzymatic hydrolysis of the acetate, (±)-**4a**, in aqueous–organic medium and the transesterification experiments with (±)-**1** in non aqueous solvents using vinyl acetate furnished **4a** and **1** in high ee. In the enzymatic kinetic resolution of (±)-4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-**4a**, high enantioselectivities can be achieved by an appropriate choice of the solvents. According to the current results, we can safely conclude that the method we introduced for the synthesis of both enantiomers of **1** and **4a** in high ee is indeed a very valuable one for the synthesis of benzopyran type building blocks. Hydrolysis of 4-oxo-3,4-dihydro-2-thiochromen-3-yl acetate did not work under these conditions.

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 m). 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 chiral column.

4.2. General procedures

4.2.1. General procedure for $Mn(OAc)_3$ oxidation. A solution of **3a** or **3b** (22.3 mmol), $Mn(OAc)_3$ (17.2 g, 66.9 mmol) and cyclohexane or benzene (200 mL) was 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 (±)-**4a** and (±)-**4b**.

4.2.1.1. Synthesis of 4-oxo-3,4-dihydro-2-chromen-3-yl acetate, (±)-4a.[14] 3.7 g (82%) colorless solid; mp 79–80°C (lit.[14] 74°C; ^{1}H NMR δ 2.1 (s, 3H), 4.3 (dd,

$J=11.2$ and 11.3 Hz), 4.5 (dd, $J=11.2$ and 5.5 Hz), 5.6 (dd, $J=11.4$ and 5.5 Hz), 6.8 (d, $J=8.4$ Hz), 6.9 (dd, $J=7.5$ and 7.4 Hz), 7.4 (dd, $J=8.4$ and 7.1 Hz), 7.8 (d, 7.8 Hz); ^{13}C NMR ($CDCl_3$+CCl_4) *d* 187.8, 169.3, 161.6, 136.6, 128.0, 122.3, 120.3, 118.1, 69.7, 68.6, 20.8.

4.2.1.2. Synthesis of 4-oxo-3,4-dihydro-2-thiochromen-3-yl acetate, (±)-4b.[14] 4.4 g (89%) colorless solid; mp 79–80°C [lit.[14] 78–80°C); ^{1}H NMR: *d* 2.2 (s, 3H), 3.1 (dd, $J=12.6$ and 4.5 Hz), 3.5 (dd, $J=13.2$ and 12.9 Hz), 5.7 (dd, $J=13.5$ and 4.5 Hz), 7.2 (m, 2H), 7.4 (dd, $J=7.9$ and 7.3 Hz), 8.0 (d, $J=7.9$ Hz); ^{13}C NMR ($CDCl_3$+CCl_4) δ 188.6, 169.0, 140.5, 133.5, 130.4, 129.9, 126.9, 125.1, 73.1, 30.1, 20.5.

4.2.1.3. Synthesis of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one, (±)-1.[6] 771 mg (94%) yellow solid, mp 57–58°C (lit.[6c] 56–57.5°C); ^{1}H NMR δ 3.7 (s, OH), 4.1 (m, 1H), 4.5 (m, 2H), 6.8 (d, $J=8.3$ Hz), 6.9 (dd, $J=7.2$ and 7.3 Hz), 7.4 (dd, $J=7.2$ and 7.1 Hz) 7.8 (d, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$+CCl_4) *d* 194.5, 162.5, 136.8, 127.7, 122.1, 119.2, 118.2, 70.9, 69.4.

4.2.2. General procedure for the lipase-catalyzed asymmetric hydrolysis of (±)-4a. Lipase (200–300 mg) was dissolved in potassium phosphate buffer (20 mM, pH 7, 50 ml) and added to a solution of the pure substrate (±)-**4** (412 mg; 2 mmol) in organic solvent (10 ml) and the reaction mixture was stirred 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 (−)-**4a** (148 mg, 36%) and the product (+)-**1** (143 mg, 44%) were separated by flash chromatography over silica (*n*-hexane/ethyl acetate, 4:1). HPLC: Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 9:1, flow 0.8 ml min^{-1}; R_f for (−)-**4a**: 12.1 min; $[\alpha]_D^{20}=-63$ (*c* 0.5 $CHCl_3$); (+)-**4a**: 13.2 min); $[\alpha]_D^{20}=61$ (*c* 0.4 $CHCl_3$); R_f for (+)-**1**: 21.4 min; $[\alpha]_D^{20}=54$ (*c* 2 $CHCl_3$); (−)-**1**: 23.4 min; $[\alpha]_D^{20}=-57$ (*c* 2 $CHCl_3$).[15]

4.2.3. General procedure for the lipase-catalyzed asymmetric transesterification of (±)-1. Racemic alcohol **1** (328 mg, 2 mmol) and isopropenyl acetate (435 mg, 4 mmol) were dissolved toluene (8 ml) and lipase (200–300 mg) was added. The reaction mixture was stirred at rt. The reaction was monitored by TLC and HPLC and when maximum conversion was reached, the reaction was terminated by filtration. Substrate (−)-**1** (128 mg, 39%) and product (+)-**4a** (177 mg, 43%) were separated by flash chromatography over silica (*n*-hexane/ethyl acetate, 4:1).

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15. The specific rotation values for **1** and **4** are not reported in the literature.