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Dynamic kinetic resolution of γ-hydroxy acid derivatives

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Abstract—Enzymatic resolution and dynamic kinetic resolution of γ-hydroxy acid derivatives **1** have been investigated. Efficient kinetic resolution was obtained using *Pseudomonas cepacia* lipase in toluene (*E* value ~400). The combination of enzymatic kinetic resolution with a ruthenium-catalyzed racemization resulted in an efficient dynamic kinetic resolution. The use of a hydrogen source to depress ketone formation in the dynamic kinetic resolution yields the corresponding acetates in good yield (up to 93%) and enantioselectivity (up to 99%).

During the last decade dynamic kinetic resolution (DKR) has become an active and important area of research in organic synthesis.[1] DKR is a powerful tool to prepare enantiomerically enriched compounds in high yields[1] that overcome the limitation of the maximum 50% yield in the traditional kinetic resolution (KR).

One of the easiest approaches to perform DKR is the combination of the traditional enzymatic kinetic resolution with an in situ racemization of the substrate using a transition metal catalyst.[2] Recently, we and others have applied this strategy in the DKR of secondary alcohols by combining a lipase-catalyzed transesterification with a ruthenium-catalyzed racemization.[2d–n]

The importance of optically active γ-hydroxy acid derivatives as chiral building blocks in the synthesis of natural products and enantiomerically enriched lactones is well established.[3] Several approaches for the preparation of enantiomerically pure γ-hydroxy acid derivatives have been developed.[4] Among them, microbial or enzymatic reductions have played a dominant role.[4c,d] Lipase-catalyzed kinetic resolutions can be useful alternatives, especially because coenzyme regeneration, an inherent problem of enzymatic redox-reactions, is not required.[5] To the best of our knowledge, only a few examples of lipase-catalyzed kinetic resolution of γ-hydroxy acid derivatives via either esterification or transesterification have been reported.[3d,6] In connection with previous work on dynamic kinetic resolution of alcohol derivatives[2d–f,j,k,m,n] we now report our novel results on kinetic and dynamic kinetic resolution of γ-hydroxy acid derivatives.

γ-Hydroxy acid esters constitute a more challenging class of substrates than for example α- and β-hydroxy acid esters due to their high tendency to undergo lactonization. Preliminary experiments using ethyl 4-hydroxypentanoate showed that both enzymatic and non-enzymatic lactonization occurred under standard dynamic kinetic resolution conditions (vide infra).[7] In order to avoid the enzymatic lactonization, the ethyl group in the latter substrate was changed to a larger, more sterically hindered *tert*-butyl ester **1a**. This significantly improved the outcome of the reaction but the non-enzymatic lactonization leading to racemic lactone was still a competing reaction.[8] For this purpose, we also investigated the use of the sterically hindered *N*,*N*-diisopropyl-4-hydroxypentanamide (**1b**), since amides are known to be less reactive than their corresponding esters.

The main requirement for an efficient DKR is that the KR conditions should be compatible with the in situ racemization process. Therefore, we screened different

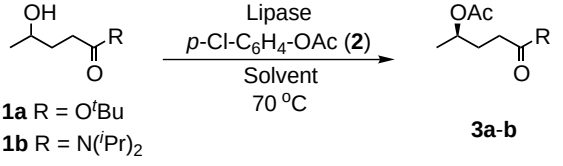

Figure 1. Kinetic resolution of γ-hydroxy acid derivatives.

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lipases in the KR of **1** under various reaction conditions, using *p*-chlorophenyl acetate (**2**) as the acyl donor (Fig. 1).[9] The latter is known to be compatible with ruthenium-catalyzed racemization of alcohols.[2d,e] The results are summarized in Table 1.

In a first set of experiments, we screened different lipases for the KR of **1a** in toluene. Even though *Candida antarctica* lipase B (N-435) showed the highest activity (entry 2), the best enantiomeric ratio (*E*) was obtained using *Pseudomonas cepacia* lipase (PS-C, entry 3). *Pseudomonas fluorescens* lipase (PF) showed good activity but the enantiomeric ratio was very low (entry 1). It is known that lipase-catalyzed kinetic resolutions can be greatly influenced by solvent variation.[10] Therefore, we studied the solvent effect in the PS-C catalyzed transesterification of **1a** (entries 3–6). Although reaction rates were similar in all the solvents, the best enantiomeric ratio was observed in toluene (entry 3). Similarly, for substrate **1b** the combination of *Pseudomonas species* lipase (PS-C) and toluene as solvent showed the best enantiomeric ratio.

On the basis of our preliminary results on KR, we combined the KR of γ-hydroxy acid derivatives **1** using lipase PS-C and the acyl donor **2** with a ruthenium-catalyzed racemization process via hydrogen transfer with the dimeric Ru-precatalyst **5**[11] (Fig. 2). The results are summarized in Table 2. Under 'standard' DKR conditions,[12] the formation of large amounts of the corresponding ketone **4** was observed (Table 2, entries 1 and 5). The latter is formed in the racemization process. Therefore, the use of a hydrogen source was needed to shift the equilibrium back to alcohol **1**. Several hydrogen donors including molecular hydrogen itself were tried.

The equilibrium between **4a** and **1a** was successfully shifted towards the alcohol **1a** by the use of hydrogen gas (1 bar). However, the racemization became slower resulting in a drop of enantioselectivity (Table 2, entry 2). In order to improve the enantioselectivity it was necessary to increase the relative rate of the racemization compared to acylation. This was accomplished by reducing the enzyme/ruthenium catalyst ratio, which increased the enantiomeric excess of **3a** to 89% (Table 2, entry 3). Further improvement of the enantioselectivity was obtained when the reaction was carried out at 60°C (Table 2, entry 4).[13]

The DKR of *N*,*N*-diisopropyl-4-hydroxypentanamide (**1b**) followed the same general trend as observed for substrate **1a**, but the efficiency of the process was improved and no lactonization was observed with this substrate (Table 2, entries 5–8). Thus, acetate **3b** was obtained in good yield (up to 93%) and high enantiomeric excess (up to 99%) when molecular hydrogen or 2,4-dimethyl-3-pentanol (**6**) was used as hydrogen donor.

Comparing the dynamic kinetic resolution results with those obtained by kinetic resolution, the efficiency of the former method is striking: the yields are higher in the dynamic process and the enantioselectivity is good to excellent.

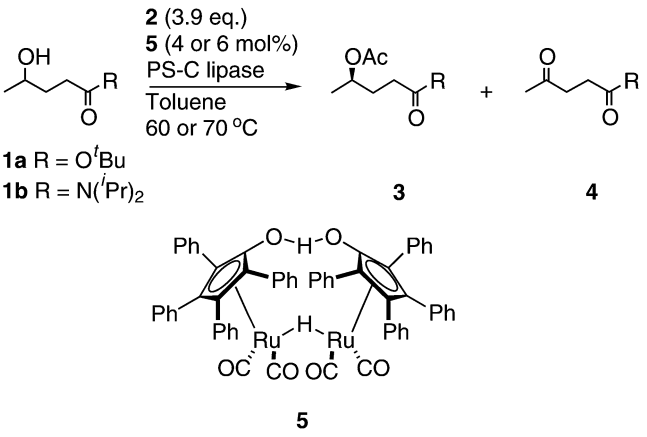

Figure 2. Dynamic kinetic resolution of γ-hydroxy acid derivatives **1a** and **1b**.

Table 1. Kinetic resolution of compound **1a** and **1b**[a]

Entry	Enzyme[b]	Solvent	Substrate	% **3**[c]	% ee[d]	*E*[e]
1	PF	$PhCH_3$	**1a**	55	9	1.3
2[f]	N-435	$PhCH_3$	**1a**	51	67	10
3	PS-C	$PhCH_3$	**1a**	52	89	68
4	PS-C	^{t}BuOMe	**1a**	56	77	34
5	PS-C	C_6H_{12}	**1a**	54	80	31
6	PS-C	EtOAc	**1a**	44	93	60
7	N-435	$PhCH_3$	**1b**	58	30	3
8[g]	PS-C	$PhCH_3$	**1b**	41	99	400[h]

[a] Unless otherwise noted, all reactions were performed on a 0.2 mmol scale for 4 h using 20 mg of enzyme (for a typical experiment see Ref. 9).
[b] PF = *Pseudomonas fluorescens* lipase, N-435 = *Candida antarctica* lipase B, PS-C = *Pseudomonas cepacia* lipase.
[c] Determined by ^{1}H NMR.
[d] Determined by GC using a CP-Chirasil-Dex CB column using racemic compounds as references.
[e] Enantiomeric ratio.[10]
[f] After 20 min.
[g] After 24 h, 1 mg of enzyme.
[h] Estimated error ±30.

Table 2. Dynamic kinetic resolution of compounds **1**[a]

Entry	Substrate	H-source[b]	*T* (°C)	% **3**[c]	% **4**[c]	% ee[d]
1	**1a**	–	70	43	50	93
2	**1a**	H_2	70	80	3	71
3[e]	**1a**	H_2	70	65	4	89
4[f]	**1a**	H_2	60	70	3	94
5	**1b**	–	70	57	43	99
6	**1b**	H_2	70	89	3	96
7[g]	**1b**	H_2	70	70	10	98
8[h]	**1b**	**6**	70	77	10	98
9[h,i]	**1b**	**6**	70	93	2	98

[a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale for 48 h using 5 mg of enzyme as described for the typical experiment in Ref. 12.
[b] H_2 (1 bar) was added in the beginning and **6** was added after 24 h.
[c] Determined by ^1H NMR.
[d] Determined by GC using a CP-Chirasil-Dex CB column.
[e] 1 mg of enzyme and 6 mol% of **5**.
[f] 3 mg of enzyme and 6 mol% of **5**.
[g] 4 mg of enzyme and 6 mol% of **5**, yield determined after 96 h.
[h] After 24 h reaction time 0.5 equiv. of 2,4-dimethyl-3-pentanol (**6**) was added.
[i] The reaction was performed on a 0.8 mmol scale using 6 mol% of **5**; yield determined after 72 h.

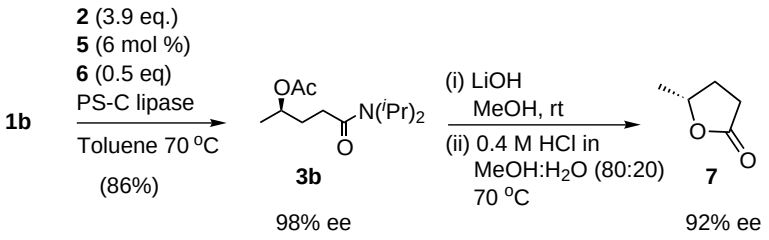

Figure 3. Synthesis of lactone **7** from racemic alcohol **1b**.

This new DKR procedure was applied to the practical synthesis of the versatile intermediate (*R*)-5-methyltetrahydrofuran-2-one (**7**).[14] The hydrogen source used in this reaction was 2,4-dimethyl-3-pentanol (**6**). In our group we have recently discovered that **6** is compatible with the enzymatic DKR as a mild and efficient hydrogen source. Thus, the enantiomerically enriched acetate **3b** was isolated in 86% yield from **1b** on a 0.8 mmol scale with an enantioselectivity of 98% following the general procedure of Ref. 12. Acetate **3b** was transformed to the (*R*)-lactone **7** via a one-pot two-step procedure involving hydrolysis with LiOH in methanol followed by acid-catalyzed lactone formation (Fig. 3). The ee of **7** was determined by chiral GC and the absolute configuration was established by comparison with literature data.[15]

In summary, we have demonstrated that ruthenium- and enzyme-catalyzed dynamic kinetic resolution of substrates **1a** and **1b** is a valuable tool for preparing enantiomerically enriched γ-hydroxy acid derivatives in good yields in a single step. This provides an easy and straightforward method to synthesize the corresponding enantiomerically enriched lactones. We also reported the potential use of alcohol **6** as a mild hydrogen source in the DKR process. Further studies to investigate the scope and limitations of this procedure are on the way.

Acknowledgements

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8. Small amounts of water (0.3–0.6%) increases the lactonization dramatically.
9. In a typical experiment **1** (0.2 mmol) and *p*-ClC_6H_4OAc **2** (132 mg, 3.9 equiv.) in solvent (2 ml) was degassed with argon for 1 min and added to a Schlenk tube containing enzyme (20 mg). The mixture was stirred under an argon atmosphere at 70°C for 4 h. The mixture was filtered through a silica pad to remove the enzyme and washed with Et_2O (3×3 ml), the solvent was evaporated and the residue was analyzed with GC and ^1H NMR.
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12. (a) In a typical experiment **1** (0.1 mmol) and *p*-ClC_6H_4OAc **2** (66 mg, 0.39 mmol) in toluene (1 ml) was degassed with argon for 1 min and added to a Schlenk tube containing PS-C (5 mg) and the ruthenium catalyst **5** (5.4 mg, 4 mol%). The mixture was stirred at 70°C for 48 h. The mixture was filtered through a silica pad to remove the enzyme and washed with Et_2O (3×3 ml), the solvent was evaporated and the residue was analyzed with GC and ^1H NMR; (b) In the 0.8 mmol experiment (Fig. 3) **1b** (161 mg, 0.8 mmol), **2** (528 mg, 3.1 mmol), **5** (65 mg, 6 mol%), and PS-C (40 mg) in toluene (8 mL) were used. After 24 h **6** (56 μl, 0.4 mmol) was added and the reaction was stirred for another 48 h.
13. The optimum performance of the PS-C is set to 55–60°C. PS-C product sheet from Amano Pharmaceutical Co. Ltd, Japan.
14. For example see: (a) Mori, K. *Tetrahedron* **1975**, *31*, 3011; (b) Imagi, S.; Wada, S.; Ito, N.; Hasebe, A. JP 11189783, 1999.
15. Compound **7** is the *R*-(+) enantiomer. The *S*-(−) enantiomer was prepared by an independent method according to Ref. 6e.