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Kinetic Resolution and Chemoenzymatic Dynamic Kinetic Resolution of Functionalized γ-Hydroxy Amides

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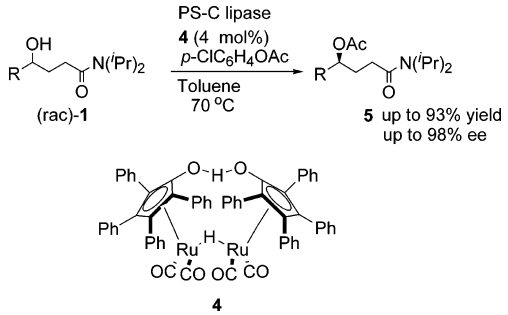

An efficient kinetic resolution of racemic γ-hydroxy amides **1** was performed via *Pseudomas cepacia* lipase (PS-C)-catalyzed transesterification. The enzyme PS-C tolerates both variation in the chain length and different functionalities giving good to high enantioselectivity (*E* values of up to >250). The combination of enzymatic kinetic resolution with a ruthenium-catalyzed racemization led to a dynamic kinetic resolution. The use of 2,4-dimethyl-3-pentanol as a hydrogen source to suppress ketone formation in the dynamic kinetic resolution yields the corresponding acetates in good yield and good to high enantioselectivity (ee's up to 98%). The synthetic utility of this procedure was illustrated by the practical synthesis of the versatile intermediate γ-lactone (*R*)-5-methyltetrahydrofuran-2-one.

Introduction

The importance of enantiomerically enriched γ-hydroxy acid derivatives as precursor of versatile building blocks in asymmetric synthesis is well established. Perhaps the most important products that can be synthesized from γ-hydroxy acid derivatives are the corresponding γ-lactones. Chiral γ-lactones are present in a large variety of natural products (e.g., fragrances, attractants, and pheromones). In addition, they are important structural elements for the synthesis of natural products and biologically active compounds.[1] Several approaches for the preparation of enantiomerically pure γ-hydroxy acid derivatives have been developed.[2] Among them, microbial or enzymatic reductions have played a dominant role.[2c,d] Lipase-catalyzed kinetic resolutions can be useful alternatives, especially because coenzyme regeneration, an inherent problem of enzymatic redox reactions, is not required.[3]

In the past few years, only a few studies dealing with lipase-catalyzed kinetic resolution (KR) of γ-hydroxy acid derivatives via either esterification or transesterification have been reported.[1e,4] However, the efficiency of the KR is limited to a maximum yield of 50%. By applying dynamic kinetic resolution (DKR) this limitation can be

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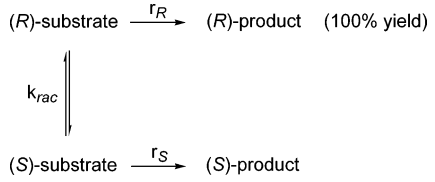
SCHEME 1. Principle of Dynamic Kinetic Resolution



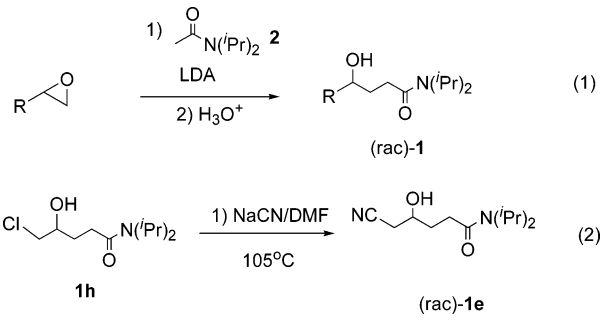
overcome.[5] With DKR, the unreactive enantiomer is continuously racemized and the desired enantiomer can be theoretically obtained in 100% yield and 100% ee. In a good DKR process the rate of racemization should be higher than the rate of product formation, r_R, r_S, and the reaction rate of one of the enantiomers should be considerably faster than that of the other ($r_R \gg r_S$) (Scheme 1).

However if the enantiomeric ratio (E) is very high, the racemization may be slower than r_R, although, in all cases the racemization has to be faster than r_S.

We and others have recently developed an easy approach to perform DKR on secondary alcohols in which the traditional enzymatic kinetic resolution is combined with an in situ racemization of the substrate using a metal catalyst.[6] Following our ongoing project dealing with the DKR of different functionalized alcohols,[7] we decided to study the DKR of γ-hydroxy carboxylic acid derivatives, which would lead to interesting building blocks for the synthesis of high-value compounds. We easily envisaged the DKR of γ-hydroxy esters, but the efficiency of the DKR of γ-hydroxy esters was low, due to their high tendency to undergo enzymatic and nonenzymatic lactonization. However, we could perform an efficient KR and DKR on the sterically hindered *N,N*-diisopropyl-4-hydroxypentanamide (**1a**).[8] We now report on the scope of the KR and DKR of sterically hindered γ-hydroxy amides. The viability of this strategy is illustrated by the practical synthesis of (*R*)-5-methyltetrahydrofuran-2-one.

Result and Discussion

Synthesis of Starting Materials. The requisite racemic γ-hydroxy amides were prepared according to two different methods. In the first method, reaction of a monosubstituted epoxide with the lithium enolate of *N,N*-diisopropylacetamide (**2**) afforded the γ-hydroxy amides in moderate to good yields (eq 1).[9] In the second method **1h** was transformed into **1e** (eq 2).[10]



Kinetic Resolution. To achieve an efficient DKR, the basic requirement is that the KR conditions should be compatible with the in situ racemization process. Therefore, 4-chlorophenyl acetate (**3**) was chosen as the primary acyl donor, since it is known to be compatible with the ruthenium-catalyzed racemization of alcohols.[6e] The use of vinyl acetate or isopropenyl acetate, commonly used as an acyl donor, results in the formation of acetaldehyde and acetone, respectively, after the acyl transfer process, which can interfere with the Ru catalyst **4**[11] usually employed in the DKR. The use of these acyldonors in DKR requires very dry conditions and a hydrogen donor.[12] In a first set of experiments, the efficiency of several commercially available lipases to catalyze the transesterification of γ-hydroxy amides **1** was investigated. For this purpose, racemic *N,N*-diisopropyl-4-hydroxypentanamide (**1a**) was chosen as model substrate.

From the enzymes tested *Candida antarctica* lipase B (Novozyme 435, N-435), *Pseudomonas species* lipase (PS-C) and *Pseudomonas fluorescens* (PF) showed good activity. Although the enzyme N-435 showed high activity, the transesterification proceeded with low enantiomeric ratio ($E = 3$). However, the enzyme PS-C showed reasonable activity and excellent enantioselectivity (Table 1, entry 2). The corresponding reaction with PF was very slow although the enantioselectivity was excellent. To obtain a reasonable rate of the acylation of **1a**, the amount of enzyme had to be increased (Table 1, entry 3). In an attempt to further enhance the acylation

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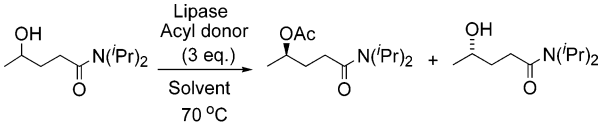
TABLE 1. Kinetic Resolution of γ-Hydroxy Amide 1a[a]

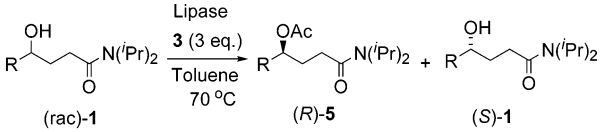


(rac)-**1a** (*R*)-**5a** (*S*)-**1a**

entry	enzyme[b]	solvent	time (h)	% of **5**[c]	% ee of **5**[d]	*E*[e]
1	CAL B	toluene	0.25	43	36	3
2	PS-C	toluene	6	41	99	>250[13]
3[f]	PF	toluene	24	47	99	>350[13]
4[f,g]	PF	toluene	8	40	98	195 ± 40
5[f,h]	PF	toluene	24	40	99	>250[13]
6	PPL	toluene	24	nr		
7	*C. rugosa*	toluene	24	nr		
8	*Aspergillus*	toluene	24	nr		
9[i]	PS-C	TBME[j]	8	48	95	113 ± 15
10	PS-C	DIPE[k]	5	49	93	83 ± 8
11	PS-C	cyclohexane	4	45	94	75 ± 5

[a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale with 5 mg of enzyme and 3 equiv of **3** in 1 mL of solvent at 70 °C. [b] CAL B = *Candida antarctica* lipase B, PS-C = *Pseudomonas cepacia* lipase, PF = *Pseudomonas fluorescens* lipase, PPL = porcine pancreas lipase, *C. rugosa* = *Candida rugosa*, *Aspergillus* = *Aspergillus* sp. [c] Determined by ^{1}H NMR. [d] Determined by GC using a CP-Chirasil-Dex CB column using racemic **1a** as reference. [e] Enantiomeric ratio[14] with estimated errors. [f] 50 mg of enzyme used. [g] Vinyl acetate was used as acyl donor. [h] Isopropenyl acetate was used as acyl donor. nr = no reaction. [i] The reaction was performed at 60 °C. [j] TBME = *tert*-butyl methyl ether. [k] DIPE = diisopropyl ether.

TABLE 2. Kinetic Resolution of γ-Hydroxy Amides 1[a]



(rac)-**1** (*R*)-**5** (*S*)-**1**

1a R = Me **1d** R = *n*-Bu **1g** R = $MeOCH_2$-

1b R = Et **1e** R = $NC-CH_2$- **1h** R = $ClCH_2$-

1c R = *n*-Pr **1f** R = CH_2=CH-CH_2-

entry	substrate	R	time (h)	% of **5**[b]	% ee of **5**[c]	*E*[d]
1	**1a**	Me−	6	41	99	>250[13]
2[e]	**1a**	Me−	24	47	99	>350[13]
3	**1b**	Et−	24	48	96	146 ± 25
4[e]	**1b**	Et−	144	35	98	168 ± 30
5	**1c**	*n*-Pr−	36	41	93	54 ± 5
6[e]	**1c**	*n*-Pr−	144	35	95	65 ± 5
7	**1d**	*n*-Bu−	144	44	nd[f]	
8	**1e**	$NCCH_2$−	24	40	95	74 ± 5
9	**1f**	CH_2=$CHCH_2$−	36	42	95	80 ± 5
10	**1g**	$MeOCH_2$−	22	43	96	106 ± 10[g]
11	**1h**	$ClCH_2$−	22	41	95	78 ± 5

[a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale with 5 mg of *Pseudomonas cepacia* lipase and 3 equiv of **3** in 1 mL of toluene at 70 °C. [b] Determined by ^{1}H NMR. [c] Determined by GC using a CP-Chirasil-Dex CB column using racemic compounds as references. [d] Enantiomeric ratio[14] with estimated errors. [e] 50 mg of *Pseudomonas fluorescens* lipase was used. [f] nd = not determined. [g] Determined by HPLC using an OJ column.

process, the more reactive acyl donors, vinyl acetate and isopropenyl acetate were used (Table 1, entries 4 and 5). In fact, using vinyl acetate enhanced the enzymatic acylation, however, a decrease in enantioselectivity was observed. The conclusion is that these acyl donors are not better than *p*-chlorophenyl acetate considering their drawbacks in the DKR process (vide supra). Other lipases examined (lipase from porcine pancreas, *Candida rugosa* and *Aspergillus* sp.) showed no reaction after 24 h (Table 1, entries 6−8). The choice of solvent is important, since the results show that the enantioselectivity of the enzyme in the acylation of **1a** is greatly dependent on the solvent. Ethers and cyclohexane gave a lower enantioselectivity compared to toluene (Table 1, entry 2 versus entries 9−11).

On the basis of the preliminary results of KR of **1a**, we applied this new procedure to a series of γ-hydroxy amides **1** with different R groups (Table 2), using toluene as solvent at 70 °C.

Our study indicates that the enantioselectivity and the activity decrease with increasing chain length (Table 2, entries 1−6). Thus, in the cases when PS-C is used as the enzyme, for methyl the *E* value was >250, whereas for ethyl and propyl it was 146 and 54, respectively. It is interesting to note that, even propyl as the small group gave a reasonable selectivity and acylation rate.[15] When the carbon chain was extended further, to the butyl group, we found that we had reached the limitation for achieving an efficient enzymatic acylation. The reaction was running for 6 days in order to achieve a reasonable yield (Table 2, entry 7). Using PF as the enzyme, the *E* value was slightly higher than for the corresponding substrates using PS-C although the acylation rate was very slow and this rules out the use of PF as an efficient enzyme in the DKR due to its lower reactivity. The KR of the functionalized substrates **1e**−**h** proceeds with high enantiomeric excess (Table 2, entries 8−11).

Dynamic Kinetic Resolution. On the basis of our preliminary results on KR, we combined the KR of γ-hydroxy amides **1** using PS-C and the acyl donor **3** with a ruthenium-catalyzed racemization process via hydrogen transfer employing the dimeric Ru-precatalyst **4** in toluene.[11c] These results are summarized in Table 3.

Under "standard" DKR conditions (i.e., 70 °C, 5 mg of PS-C and 4 mol % of **4**), formation of large amounts of the corresponding ketone **6a** was observed; the latter is formed during the hydrogen transfer process (Table 3, entry 1). Several attempts to increase the efficiency of the process by reducing the amount of ketone have been carried out. Thus, 2,4-dimethyl-3-pentanol (**7**), 2,6-dimethyl-4-heptanol (**8**), hydrogen gas (**9**), HCOOH (**10**), and HCOOH·NEt_3 (1:1) (**11**) were tested as hydrogen sources with the aim to push the equilibrium back to the alcohol **1a**. The equilibrium between the alcohol **1a** and the ketone **6a** was successfully shifted toward the alcohol

(13) Table 1, entry 2, and Table 2, entry 1: The calculated *E* value was 410 and the error was estimated to ±150. Table 1, entry 3, and Table 2, entry 2: The calculated *E* value was 580 and the error was estimated to ±200. Table 1, entry 5: The calculated *E* value was 390 and the error was estimated to ±135.

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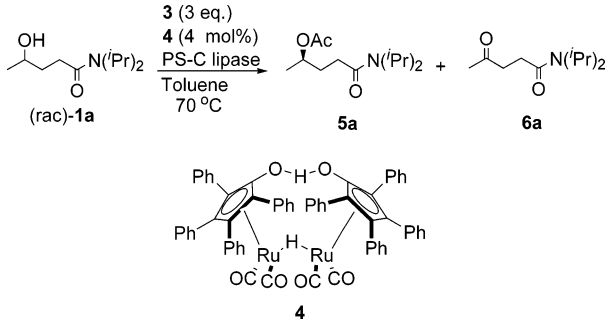
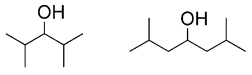
TABLE 3. Dynamic Kinetic Resolution of γ-Hydroxy Amide 1a[a]



entry	hydrogen source	time (h)	% of **5a**[b]	% of **6a**[b]	% ee[c]
1		48	57	43	99
2	**7**	48	76	11	97
3	**8**	48	79	1	96
4	**9**	48	89	3	96
5	**10**	48	nr		
6	**11**	48	48	28	95
7[d]	**7**	48	77	10	98
8[e]	**7**	48	78	11	97

[a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale for 48 h using 5 mg of *Pseudomonas cepacia* lipase, 0.5 equiv of hydrogen source, 3 equiv of **3**, and 4 mol % of **4** in 1 mL of toluene at 70 °C. [b] Determined by ^{1}H NMR. [c] Determined by GC using a CP-Chirasil-Dex CB column using racemic compounds as references. [d] 2,4-Dimethyl-3-pentanol (**7**) was added after 24 h. [e] 6 mol % of **4** was used. nr = no reaction.



H_2 (1bar) HCOOH $HCOOH{\cdot}NEt_3$

9 **10** **11**

1a with hydrogen sources **7**, **8** and **9** (Table 3, entry 1 versus entries 2−4). When **10** and **11** were used as hydrogen sources, no activity or slower reaction rate was observed and the selectivity was decreased slightly (Table 3, entries 2−4 versus entries 5−6).

Although the DKR is faster with hydrogen gas (**9**) than with **7** as a hydrogen donor (Table 3, entry 2 vs 4), the latter was chosen as a hydrogen source to perform DKR since it provided better enantioselectivity and it is a milder hydrogen donor compared to hydrogen gas.

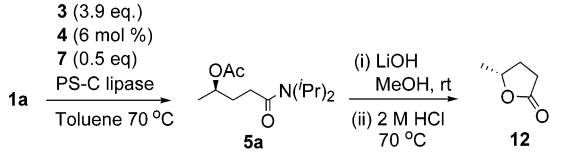
For **1a** and **1b** the same conditions were used, yielding an excellent enantioselectivity. Due to the longer carbon chain in **1b** a slower acylation (65% conversion) was observed compared to **1a** (93% conversion) after a reaction time of 72h (Table 4, entries 2 and 1, respectively). To achieve a reasonable acylation rate of **1c**, the amount of enzyme was increased, however this resulted in a decrease in enantioselectivity (Table 4, entry 3). For **1e** the DKR was unsuccessful at 70 °C and this agrees with the results of DKR of nitriles previously reported by Pàmies et al.[7e] Therefore, the reaction temperature was increased to 80 °C affording the corresponding acetate in high yield. The lower enantioselectivity in this case might be due to that the optimum temperature of the enzyme was exceeded (Table 4, entry 4).[16] In the DKR both **1g** and **1h** gave good yields and high enantioselectivities (Table 4, entries 5 and 6). Substrate **1f** was under the DKR conditions, incompatible with the racemization

TABLE 4. Dynamic Kinetic Resolution of γ-hydroxy Amides 1[a]

entry	substrate (R)	mg of enzyme[b]	% of **5**[c]	% of **6**[c]	% ee[d]
1[e]	**1a** (Me−)	5	93	2	98
2	**1b** (Et−)	5	65	10	98
3	**1c** (Pr−)	20	59	9	92
4[f]	**1e** ($NCCH_2$−)	10	90	9	80
5	**1g** (CH_3OCH_2−)	10	85	6	91[g]
6[h]	**1h** (CH_2Cl−)	5	70	1	95

[a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale for 72 h using 5 mg of PS-C lipase, 4 mol % of **4**, and 3 equiv of **3** in 1 mL of toluene at 70 °C. 2,4-Dimethyl-3-pentanol (**7**) (0.5 equiv) was added after 24 h. [b] mg enzyme/0.1 mmol substrate. [c] Determined by ^{1}H NMR. [d] Determined by GC using a CP-Chirasil-Dex CB column. [e] The reaction was performed on a 0.8 mmol scale using 3.9 equiv of **3** and 6 mol % of **4**. [f] 4 mol % of **4** was added after 14 h, and at the same time the temperature was raised to 80 °C, **7** was added after 38 h. [g] Determined by HPLC using an OJ column. [h] 4 mol % of **4** was added after 22 h, and **7** was added after 46 h.

SCHEME 2. Synthesis of Lactone 12



catalyst **4**, forming both the corresponding saturated ketone and the corresponding conjugated ketone in high yields.

Synthetic Applications. A wide range of synthetic applications of this dynamic kinetic resolution procedure can be envisaged. One example is the practical synthesis of the versatile intermediate (*R*)-5-methyltetrahydrofuran-2-one **12**.[17] Thus, the enantiomerically enriched acetate **5a** was isolated in 86% yield from **1a** on a 0.8 mmol scale with an enantioselectivity of 98%. Acetate **5a** was transformed to the (*R*)-lactone **12** via a one-pot two-step procedure involving hydrolysis with LiOH in methanol followed by acid-catalyzed lactone formation (Scheme 2). The ee of **12** was determined by chiral GC and the absolute configuration was established by comparison with literature data.[18]

Conclusions

Enantioselective transformations of important substrate class, γ-hydroxyamides, were carried out under KR and DKR conditions. PS-C allowed variations in the carbon chain attached to the γ-carbon. For a variety of substrates PS-C showed high enantioselectivity, in all cases over 93% ee. Together with a racemization catalyst **4** and a hydrogen source, an efficient DKR was achieved. The DKR gives access to enantiomerically enriched functionalized γ-acetoxyamides with yields up 90% and ee up to 95%. In conclusion, comparing the dynamic

(16) The optimum performance of the PS-C is set to 55−60 °C. PS-C product sheet from Amano Pharmaceutical Co. Ltd., Japan.

(17) For example, see: (a) Mori, K. *Tetrahedron* **1975**, *31*, 3011. (b) Imagi, S.; Wada, S.; Ito, N.; Hasebe, A. JP 11189783, 1999.

(18) Compound **12** is the *R*-(+) enantiomer. The *S*-(−) enantiomer was prepared by an independent method according to ref 4e for the assignment of the absolute configuration.

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

Experimental Section

Synthesis of γ-Hydroxy Amides. *N,N*-Diisopropyl-4-hydroxypentanamide (1a). General Method. To a solution of diisopropylamine (1.44 mL, 10.0 mmol) in dry THF (10.0 mL) under argon atmosphere at 0 °C was added *n*-BuLi (6.25 mL, 10.0 mmol) in *n*-hexane dropwise. The reaction was stirred at 0 °C for 5 min and for an additional 5 min at room temperature. The solvent was evaporated, and THF (15 mL) was added followed by dropwise addition of *N,N*-diisopropylacetamide (1.6 mL, 10.0 mmol) at 0 °C. The solution was stirred for 10 min at 0 °C, and Et_2AlCl 1M in *n*-hexane (6.0 mL, 6.00 mmol) was added. The epoxide (0.75 mL, 11.0 mmol) was added, and the mixture was stirred at 0 °C for 30 min and then at reflux for 2 h. The reaction was cooled to room temperature and quenched with 1 M acetic acid in ether (10 mL). The salts were filtered off, and the γ-hydroxy amide was purified by flash chromatography.

5-Cyano-*N,N*-diisopropyl-4-hydroxypentanamide (1e). NaCN (2.00 mmol) was added at room temperature to a solution of **1h** (231 mg, 0.98 mmol) in DMF (15 mL), and the resulting mixture was heated with stirring at 105 °C for 4 h. After the reaction was cooled, the DMF was evaporated and the residue was dissolved with water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, evaporated, and purified by flash chromatography (pentane/EtOAc 1:1) to give **1e** (155 mg, 70%) as a colorless oil.

Hydroxyamides **1a**−**d** and **1f**−**h** were prepared according to the general method.

***N,N*-Diisopropyl-4-hydroxypentanamide (1a).** Flash chromatography (pentane/EtOAc 1:3) gave **1a** (1.42 g, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.99 (sept, J = 6.9, 1H), 3.90−3.75 (m, 1H), 3.59−3.40 (m, 2H), 2.57−2.36 (m, 2H), 1.84−1.67 (m, 2H), 1.37 (d, J = 6.9, 6H), 1.29−1.13 (m, d, J = 6.9, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 68.6, 48.5, 45.7, 33.8, 31.9, 23.7, 20.9 (2 C), 20.6, 20.5.

***N,N*-Diisopropyl-4-hydroxyhexanamide (1b).** Flash chromatography (pentane/EtOAc 1:3) gave **1b** (1.52 g, 70%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.96 (sept, J = 6.9, 1H), 3.53−3.31 (m, 3H), 2.48−2.38 (m, 2H), 1.83−1.59 (m, 2H), 1.50−1.39 (m, 2H), 1.32 (d, J = 6.9, 6H), 1.15 (d, J = 6.9, 6H), 0.89 (dt, J = 7.5, 2.3, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 73.0, 48.4, 45.7, 32.0, 31.4, 30.6, 20.8 (2 C), 20.6, 20.5, 9.9.

***N,N*-Diisopropyl-4-hydroxyheptanamide (1c).** Flash chromatography (pentane/EtOAc 1:1) gave **1c** (0.68 g, 30%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.99 (sept, J = 6.9, 1H), 3.64−3.54 (m, 1H), 3.54−3.43 (m, 1H), 3.40 (d, J = 3.9, 1H), 2.55−2.38 (m, 2H), 1.85−1.64 (m, 2H), 1.51−1.29 (m, d, J = 6.9, 10H), 1.19 (d, J = 6.9, 6H), 0.91 (t, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 71.6, 48.7, 46.0, 40.3, 32.3, 32.2, 21.1 (2 C) 20.8, 20.7, 19.1, 14.3. HRMS (*m/z*) calcd for $C_{13}H_{28}NO_2$ $(M + H)^+$ 230.2120, found 230.2128.

***N,N*-Diisopropyl-4-hydroxyoctanamide (1d).** Flash chromatography (pentane/EtOAc 1:1) gave **1d** (1.05 g, 43%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.00 (sept, J = 6.6, 1H), 3.63−3.54 (m, 1H), 3.54−3.40 (m, 1H), 3.36 (d, J = 4.5, 1H), 2.56−2.40 (m, 2H), 1.85−1.66 (m, 2H), 1.51−1.26 (m, d, J = 6.7, 12H), 1.20 (d, J = 6.7, 6H), 0.89 (t, J = 6.7, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 71.7, 48.5, 45.8, 37.6, 32.1, 32.0, 27.9, 22.8, 20.9 (2 C) 20.6, 20.5, 14.1.

5-Cyano-*N,N*-diisopropyl-4-hydroxypentanamide (1e). Flash chromatography (pentane/EtOAc 1:1) gave **1e** (0.155 g, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.03−3.90 (m, 2H), 3.60−3.43 (m, 1H), 2.73−2.43 (m, 4H), 2.00−1.93 (m, 2H), 1.37 (dd, J = 6.7, 2.1, 6H), 1.22 (dd, J = 6.7, 2.1, 6H); ^{13}C NMR ($CDCl_3$) δ 172.5, 117.8, 68.1, 48.7, 46.2, 32.0, 30.8, 26.3, 20.7 (2 C), 20.5, 20.4. HRMS (*m/z*) calcd for $C_{12}H_{23}N_2O_2$ $(M + H)^+$ 227.1760, found 227.1763.

***N,N*-Diisopropyl-4-hydroxyhept-6-enamide (1f).** From the general method using 4,5-epoxy-1-pentene.[19] Flash chromatography (pentane/EtOAc 2:3) gave **1f** (0.453 g, 20%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.91−5.79 (m, 1H), 5.14−5.06 (m, 2H), 3.99 (sept, J = 6.7 1H), 3.71−3.62 (m, 1H), 3.55−3.40 (m, 2H), 2.56−2.40 (m, 2H), 2.25 (t, J = 7.2, 2H), 1.89−1.70 (m, 2H), 1.36 (d, J = 6.7, 6H), 1.20 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 172.5, 135.1, 117.4, 70.9, 48.5, 45.8, 42.4, 32.0, 31.4, 20.9 (2 C) 20.7, 20.6.

***N,N*-Diisopropyl-4-hydroxy-5-methoxypentanamide (1g).** Flash chromatography (pentane/EtOAc 4:1 to 1:3) gave **1h** (0.97 g, 42%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.99 (sept, J = 6.7, 1H), 3.81−3.72 (m, 1H), 3.63 (d, J = 3.3, 1H), 3.54−3.42 (m, 1H), 3.39−3.28 (m, 5H), 2.48 (t, J = 6.7, 2H), 1.90−1.64 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.18 (d, J = 6.9, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 77.0, 70.1, 59.1, 48.4, 45.7, 31.5, 28.4, 20.9 (2 C), 20.6, 20.5.

5-Chloro-*N,N*-diisopropyl-4-hydroxypentanamide (1h). Flash chromatography (pentane/EtOAc 1:2) gave **1i** (0.81 g, 35%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.51 (d, J = 4.1, 1H), 3.98 (sept, J = 6.9, 1H), 3.86−3.74 (m, 1H), 3.61−3.41 (m, 3H), 2.66−2.52 (m, 1H), 2.52−2.39 (m, 1H), 2.03−1.79 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.20 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 71.6, 49.3, 48.6, 46.0, 31.6, 28.9, 20.8 (2 C), 20.6, 20.5; HRMS (*m/z*) calcd for $C_{11}H_{23}ClNO_2$ $(M + H)^+$ 236.1417, found 236.1417.

General Procedure for Synthesis of Racemic γ-Acetoxy Amides (5). To a solution of the appropriate hydroxyamide **1** (0.5 mmol) in dichloromethane (2.5 mL) were added triethylamine (0.5 mL) and acetic anhydride (0.5 mL) at 0 °C. The reaction was stirred at room temperature overnight. The solution was evaporated and purified by flash chromatography. The yields of acetoxyamides **5** were >95%.

4-Acetoxy-*N,N*-diisopropylpentanamide (5a): ^{1}H NMR ($CDCl_3$) δ 4.98−4.89 (m, 1H), 3.93 (sept, J = 6.9, 1H), 3.60−3.41 (m, 1H), 2.38−2.23 (m, 2H), 2.03 (s, 3H), 1.95−1.82 (m, 2H), 1.36 (d, J = 6.7, 6H), 1.24 (d, J = 6.2, 3H), 1.19 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.7, 70.7, 48.1, 45.6, 31.4, 31.0, 21.3, 20.9 (2 C), 20.6 (2 C), 20.1.

4-Acetoxy-*N,N*-diisopropylhexanamide (5b): ^{1}H NMR ($CDCl_3$) δ 4.87−4.78 (m, 1H), 3.91 (sept, J = 6.9, 1H), 3.58−3.34 (m, 1H), 2.31−2.24 (m, 2H), 2.04 (s, 3H), 1.98−1.74 (m, 2H), 1.57 (dq, J = 7.4, 1.1, 2H), 1.35 (d, J = 6.7, 6H), 1.17 (d, J = 6.7, 6H), 0.89 (t, J = 7.4, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2 (2 C), 75.2, 48.2, 45.7, 31.2, 29.3, 27.3, 21.2, 20.8 (2 C), 20.6 (2 C), 9.6.

4-Acetoxy-*N,N*-diisopropylheptanamide (5c): ^{1}H NMR ($CDCl_3$) δ 4.98−4.85 (m, 1H), 3.91 (sept, J = 6.9, 1H), 3.60−3.33 (m, 1H), 2.32−2.22 (m, 2H), 2.04 (s, 3H), 1.99−1.74 (m, 2H), 1.61−1.44 (m, 2H), 1.41−1.24 (m, d, J = 6.7, 8H), 1.17 (d, J = 6.7, 6H) 0.89 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 170.8, 73.8, 48.1, 45.6, 36.5, 31.0, 29.7, 21.2, 20.9 (2 C), 20.7, 20.6, 18.5, 13.9.

4-Acetoxy-*N.N*-diisopropyl-octanamide (5d): ^{1}H NMR ($CDCl_3$) δ 4.93−4.85 (m, 1H), 3.92 (sept, J = 6.4, 1H), 3.58−3.37 (m, 1H), 2.31−2.24 (m, 2H), 2.04 (s, 3H), 1.98−1.75 (m, 2H), 1.63−1.47 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.33−1.23 (m, 4H), 1.18 (d, J = 6.7, 6H), 0.87 (t, J = 6.7, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0 (2C), 74.1, 48.1, 45.6, 34.1, 31.1, 29.7, 27.4, 22.5, 21.2, 20.9 (2 C,), 20.6 (2 C), 13.9.

4-Acetoxy-5-cyano-*N,N*-diisopropylpentanamide (5e): ^{1}H NMR ($CDCl_3$) δ 5.11−5.02 (m, 1H), 3.90 (sept, J = 6.7, 1H), 3.54−3.38 (m, 1H), 2.77 (dd, J = 17, 5.1, 1H), 2.65 (dd, J = 17, 5.1, 1H), 2.34 (t, J = 7.1, 2H), 2.09 (s, 3H), 2.08−1.95 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.18 (dd, J = 6.7, 2.9, 6H); ^{13}C NMR ($CDCl_3$) δ 170.2, 169.6, 116.3, 68.4, 48.2, 45.7, 30.2, 28.9, 23.2, 20.9, 20.8 (2 C), 20.6, 20.5.

(19) Schuda, A. D.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309.

4-Acetoxy-*N*,*N*-diisopropylhept-6-enamide (5f): ^{1}H NMR ($CDCl_3$) δ 5.82−5.65 (m, 1H), 5.12−4.99 (m, 2H), 4.99−4.86 (m, 1H), 3.90 (sept, J = 6.7, 1H), 3.56−3.37 (m, 1H), 2.36−2.22 (m, 4H), 2.02 (s, 3H), 1.99−1.74 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.17 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.7, 133.4, 117.8, 73.0, 48.1, 45.6, 38.9, 31.0, 29.3, 21.2, 20.9 (2 C) 20.7, 20.6; HRMS (*m/z*) calcd for $C_{15}H_{28}NO_3$ $(M + H)^+$ 270.2069, found 270.2059.

4-Acetoxy-*N*,*N*-diisopropyl-5-methoxypentanamide (5g): ^{1}H NMR ($CDCl_3$) δ 5.11−5.01 (m, 1H), 3.92 (sept, J = 6.9, 1H), 3.55−3.40 (m, 3H), 3.34 (s, 3H), 2.30 (t, J = 7.7, 2H), 2.07 (s, 3H), 2.04−1.80 (m, 2H), 1.35 (d, J = 6.7, 6H), 1.17 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.5, 73.9, 72.2, 59.1, 48.1, 45.6, 30.8, 26.6, 21.2, 20.9 (2 C), 20.7, 20.6; HRMS (*m/z*) calcd for $C_{14}H_{28}NO_4$ $(M + H)^+$ 274.2018, found 274.2012.

4-Acetoxy-5-chloro-*N*,*N*-diisopropylpentanamide (5h): ^{1}H NMR ($CDCl_3$) δ 5.16−5.04 (m, 1H), 3.92 (sept, J = 6.9, 1H), 3.67 (dd, J = 11.8, 4.5, 1H), 3.59 (dd, J = 11.8, 5.7, 1H), 3.55−3.38 (m, 1H), 2.37−2.28 (m, 2H), 2.09 (s, 3H), 2.07−1.86 (m, 2H), 1.36 (d, J = 6.7, 6H), 1.19 (d, J = 6.7, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.1, 72.6, 48.2, 45.9, 45.7, 30.5, 27.4, 21.0, 20.9 (2 C) 20.7, 20.6.

General Procedure for the Kinetic Resolution of γ-Hydroxy Amides. In a typical experiment, **1a** (20.1 mg, 0.1 mmol) and *p*-ClC_6H_4OAc **3** (51 mg, 0.3 mmol) in toluene (1 mL) were degassed with argon for 1 min and added to a Schlenk tube containing enzyme (5 mg). The mixture was stirred under argon atmosphere at 70 °C. The mixture was filtered through a silica pad to remove the enzyme, the solid was washed with Et_2O (3 × 3 mL), the combined solvent was evaporated, and the residue was analyzed by GC and ^{1}H NMR.

General Procedure for the Dynamic Kinetic Resolution of γ-Hydroxy Amides. In a typical experiment, **1a** (20.1 mg, 0.1 mmol) and *p*-ClC_6H_4OAc **3** (51 mg, 0.30 mmol) in toluene (1 mL) were degassed with argon for 1 min and added to an Schlenk tube containing PS-C (5 mg) and the ruthenium catalyst **4** (5.4 mg, 4 mol %). The mixture was stirred at 70 °C for 24 h, and 2,4-dimethyl-3-pentanol as a hydrogen source (0.5 equiv) was added. The mixture was stirred for another 48 h and worked up by filtering through a silica pad to remove the enzyme. The solid was washed with Et_2O (3 × 3 mL), the combined solvent was evaporated, and the residue was analyzed by GC and ^{1}H NMR.

Synthesis of (*R*)-5-Methyltetrahydrofyran-2-one (12). The enantiomerically enriched γ-acetoxy amide **5a** (125 mg, 0.51 mmol) was stirred in methanol (5 mL) together with LiOH (15.4 mg, 0.64 mmol) at room temperature. After 12 h, 2 M HCl (1.25 mL) was added. The mixture was stirred at 70 °C for 3 days, during which time additional 2 M HCl (1.45 mL) was added. The reaction mixture was cooled to room temperature and purified by bulb-to-bulb distillation, affording enantiomerically enriched **12** (44.0 mg, 86%) in 92% ee as a pale yellow oil. The spectroscopic data were in accordance with those in the literature.[4e]

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1a**−**h** and **5a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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