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Chemoenzymatic Dynamic Kinetic Resolution of Acyloins

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Received August 8, 2005

>90 % conv., >91 % ee

Acyloins (α-hydroxy ketones) are important building blocks in organic synthesis, e.g., for the total synthesis of epothilones. Optically pure acyloins can be obtained by lipase-catalyzed kinetic resolution (KR) of the racemate with, for example, *Burkholderia cepacia* lipase, but this process suffers from a yield limitation of 50%. To devise a dynamic kinetic resolution (DKR), we studied the racemization of two different acyloins and corresponding esters with various amine bases and ion exchangers. No combination of base and solvent was found that could selectively racemize the acyloin or corresponding ester under the conditions needed for a DKR. In contrast to bases, acidic resins (ARs) were found to racemize the acyloins selectively in *n*-hexane and in water. Unfortunately, the AR deactivated the lipase, preventing a one-pot DKR. Minor side reactions involving the AR, the substrate acyloin, and the vinyl ester acyl donor were also observed. However, an efficient DKR was made possible by the spatial separation of lipase and ion exchanger, with enzymatic transesterification and AR-catalyzed racemization taking place simultaneously in two compartments connected by a pump loop. The conversion of substrate alcohol was 91%, the selectivity toward the product butyrate ester 90%, and the enantiomeric excess of the (*S*)-product 93% ee.

Introduction

Today there is a great demand for optically pure specialty chemicals in, for example, the pharmaceutical industry, where the stereochemistry of the products must be carefully controlled. In a kinetic resolution (KR), a widely used method to separate the two enantiomers in a racemic mixture,[1] an enantioselective catalyst (e.g., an enzyme) reacts faster with one of the enantiomers than with the other. The main drawback of this method, which has been extensively used for the resolution of a large number of compounds, is that the product yield is limited to 50%. This can be overcome by combining the kinetic resolution with racemization of the unwanted enantiomer by using a so-called dynamic kinetic resolution (DKR). In DKR, the wanted enantiomer of the substrate is continuously being replenished via the racemization, and a (theoretical) 100% yield is possible.

Hydrolases are well suited as catalysts for resolution-type reactions.[2] The high regio- and enantioselectivity of many lipases and esterases allows for the complete separation of the enantiomers of many racemic alcohols, esters, amides, and amines. However, combining enzymatic catalysis with in situ racemization in DKR can be problematic, because many compounds only racemize under harsh conditions that are incompatible with the enzyme activity.[3] Common racemization methods include metal-,[4] base-, acid-, and enzyme-catalyzed methods,[5] along with thermal and reduction/oxidation methods.[3] Very promising results have been obtained using different lipase-compatible Ru complexes for the racemization of secondary alcohols via hydrogen transfer. Acid zeolites

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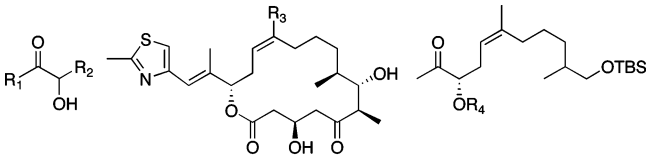
(1) Faber, K. *Chem.—Eur. J.* **2001**, *7*, 5004−5010.
(2) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis − Regio- and Stereospecific Biotransformations*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2005.
(3) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.
(4) Pamiès, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130−135.
(5) Schnell, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2003**, *345*, 653−666.

10.1021/jo051661n CCC: $30.25 © 2005 American Chemical Society
Published on Web 10/12/2005

SCHEME 1. Structures of Acyloins[a]



1 **2** **3**

[a] **1** general; **2** epothilone (R_3 = H or Me); **3** epothilone building block (R_4 = H, acetate, or butyrate).

have also recently been reported to successfully racemize benzylic secondary alcohols under conditions compatible with enzymatic catalysis.[6]

Acyloins are α-hydroxy ketones. The acyloin moiety **1** (Scheme 1) is present in a variety of natural compounds, such as antitumor agents and antibiotics.[7] It has an important function as a building block in organic synthesis, e.g., the synthesis of epothilones. Epothilones are a group of macrolide compounds, in nature synthesized by the bacterium *Sorangium cellulosum*. In vitro, they exhibit cytotoxic effects resembling those of paclitaxel (Taxol), also containing an acyloin moeity, but otherwise structurally unrelated to this compound. Moreover, the epothilones are active against multidrug-resistant cell lines, which make them especially interesting.[8]

We have previously reported the efficient lipase- and esterase-catalyzed kinetic resolution affording the enantiomerically pure (*S*)-acyloin building block **3** used for the synthesis of epothilones C and D.[9,10]

To increase the product yield in the resolution of the optically pure acyloins, we developed a route for a dynamic kinetic resolution as described in this paper.

Results

The acyloins 3-acetoxy-6-methyl-5-hepten-2-one (**4**), 3-butyroxy-6-methyl-5-hepten-2-one (**5**), 3-butyroxy-4-phenylbutan-2-one (**6**), 3-hydroxy-6-methyl-5-hepten-2-one (**7**), and 3-hydroxy-4-phenylbutan-2-one (**8**) were used in this investigation (Scheme 2).

For a dynamic kinetic resolution to be carried out, a racemization method compatible with an enzymatic reaction must be found. Three possible alternatives are shown in Scheme 3.

Enzymatic hydrolysis of **4**−**6** (acyloin esters) and esterification of acyloin **7** with vinyl acetate have previously been performed with excellent enantioselectivity.[9,10] Acyloin **8** was resolved via enzymatic transesterification with *Burkholderia cepacia* lipase (BCL) or *Candida antarctica* lipase B (CAL-B), with vinyl butyrate as the acyl donor, to see if this substrate was also suitable for that kind of reaction. The results are shown in Table 1.

TABLE 1. Results from Esterification of 8 with BCL or CAL-B and Vinyl Butyrate in *n*-Hexane

lipase	*T* (°C)	time (h)	conversion (%)	*E* value
BCL	40	15	51	>300
CAL-B	40	15	40	48
CAL-B	50	6	43	65

TABLE 2. Deacylation of Acyloin Esters in *n*-Hexane/2-Propanol (8:1) at 50 °C

acyloin ester	enzyme	conversion[a] (%)	enantiomeric excess[a] (% ee)	
			ester	alcohol
4	BCL	9	9	89
	CAL-B	26	33	94
5	BCL	5	5	100
	CAL-B	20	24	98
6	BCL	5	4	85
	CAL-B	15	13	69

[a] Conversion and enantiomeric excess were determined after 15 h.

Both BCL and CAL-B showed good enantioselectivity for this reaction. As can be seen, the 10 °C increase in temperature doubled the reaction rate of CAL-B. From Table 1, it also seems that this led to a moderate improvement in enantioselectivity.

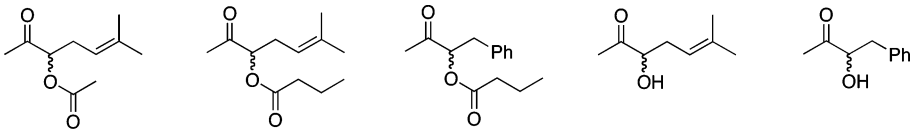
To investigate the feasibility of a DKR according to Scheme 3c, a kinetic resolution of **4**−**6** was performed in this manner. CAL-B and BCL were used for deacylation of racemic **4**, **5**, and **6** in 2-propanol. After 23 h, there was no measurable conversion catalyzed by BCL, and only ∼5% of each substrate had been converted by CAL-B. All three reactions were (*S*)-selective with CAL-B. It was suspected that the 2-propanol might inhibit the enzymes at high concentrations, and deacylation was therefore carried out in an *n*-hexane/2-propanol (8:1) mixture. The results after 15 h are shown in Table 2.

The enzymes do seem to be inhibited or deactivated by high concentrations of 2-propanol, since the reaction worked much better in the *n*-hexane/2-propanol mixture. Deactivation could be an effect of dehydration of the enzyme, and inhibition could be possible, since the substrate 2-propanol is present in high excess. *E* values could not be calculated, because the equilibrium constant for this reaction is unknown. An additional measurement was done for the reaction with CAL-B and **4**. After 22 h, the conversion was 33%, and the enantiomeric excess of alcohol was 94%, and for the remaining ester was 46%. The 33% conversion after 22 h represents a 13% decrease in reaction rate compared to the 26% conversion after 15 h. This could suggest that the enzyme is inhibited/deactivated over time, e.g., by the 2-propanol.

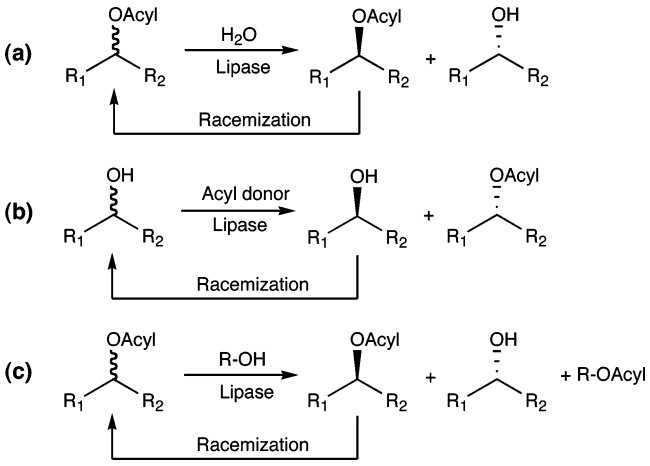
Alternatively, organic bases were investigated for the racemization efficiency in lipase-catalyzed hydrolysis reactions according to Scheme 3a. First, racemic acyloin acetate **4** was enantioselectively hydrolyzed to yield the enantioenriched alcohol (*S*)-**7** (94% ee) and ester (*R*)-**4** (99% ee) to serve as starting materials for the racemization studies. The enantioenriched acyloin and acyloin ester were together subjected to racemization with the organic bases 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD),

(6) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. *Chem.—Eur. J.* **2005**, *11*, 386−397.
(7) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934. (b) Wessjohann, L. A.; Scheid, G. Synthetic access to epothilones − natural products with extraordinary anticancer activity. In *Organic Synthesis Highlights IV*; Schmalz, H. G., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 251−267. (c) Wessjohann, L. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 715−718.
(8) Kowalski, R. J.; Giannakakous, P.; Hamel, E. *J. Biol. Chem.* **1997**, *272*, 2534−2541.
(9) Scheid, G.; Ruijter, E.; Konarzycka-Bessler, M.; Bornscheuer, U. T.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2861−2869.
(10) (a) Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R. V. A.; Henke, E.; Bornscheuer, U. T.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2004**, 1063−1074. (b) Wessjohann, L. A.; Scheid, G.; Bornscheuer, U.; Henke, E.; Kuit, W.; Orru, R. WO Pat. Appl. 2002032844; *Chem. Abstr*. **2002**, *136*, 340534.

SCHEME 2. Acyloins Used in This Work



SCHEME 3. Possible Routes for a Dynamic Kinetic Resolution[a]



[a] (a) Racemization of the acyloin ester in the presence of water, to be combined with enzymatic hydrolysis of the acyloin ester. (b) Racemization of the acyloin in organic solvent, to be combined with enzymatic transesterification of the alcohol with, for example, a vinyl ester as the acyl donor. (c) Racemization of the acyloin ester in organic solvent, to be combined with deacylation of the acyloin ester in the presence of an achiral alcohol as the acyl acceptor.

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), N,N,N′,N′-tetramethylethylenediamine (TMEDA), 1,4-diazabicyclo[2.2.2]octane (DABCO), and triethylamine (Et_3N) in different solvents, including *n*-hexane, methyl *tert*-butyl ether (MTBE), THF, H_2O, THF with 5% v/v H_2O, and 2-propanol. The results are summarized in Table 3.

Some interesting solvent effects are shown in Table 3. In *n*-hexane, TBD clearly racemizes the ester faster than it does the alcohol. When 10% MeOH is added to the *n*-hexane, the TBD effects complete methanolysis of the ester. In pure THF and MTBE, like as in *n*-hexane, it racemizes the ester preferably over the alcohol. When 5% water is added to the THF, selectivity is inverted; the TBD prefers the alcohol and leaves the ester untouched. Water seems to be a good solvent for the racemization of the alcohol form: TBD, DBU, and DBN all racemize the alcohol faster than the ester in the presence of water. It should be noted that in the case of hydrolysis of the (*R*)-ester in the presence of H_2O, a decrease of enantiopurity of alcohol would be observed. A slight decrease in ester concentration was observed in the presence of TBD and DBU (but not with DBN) in H_2O, but the possibility of ester hydrolysis was not further investigated. In TMEDA, DABCO, and Et_3N, no racemization was observed (data not shown).

Especially interesting are the racemization properties of TBD and DBU in 2-propanol. Selective racemization of the ester in the presence of an alcohol allows (in theory) for a dynamic kinetic resolution, with enzymatic deacylation of the acyloin ester yielding the ester of the achiral alcohol. Unfortunately, pure 2-propanol turned out to be a bad environment for the resolution of acyloins (see above), and a kinetic resolution is not feasible in this solvent. In an *n*-hexane/2-propanol system however, TBD and DBU are less selective and much slower than in both pure *n*-hexane and 2-propanol, though still active.

The results from these experiments with organic bases in different solvents are very interesting, and equally confusing. The different racemization behavior regarding reactivity and selectivity of the bases in different media cannot be simply related to the polarity (dielectric constant) or hydrophobicity (log *P*) of the solvent.

Next, we focused on the use of acidic resins as possible racemization agents. Enantioenriched (*S*)-acyloins and the corresponding (*R*)-esters were racemized at 50 °C with different acidic resins in different solvents. The results are presented in Table 4.

Table 4 shows that all four resins are able to selectively racemize the acyloin in H_2O and *n*-hexane, without affecting the ester. This means that it is possible to racemize the residual substrate alcohol in an enzymatic esterification in *n*-hexane. No hydrolysis of ester was observed. Table 4 also shows that the vinyl acetate is not inert in the presence of the resins, resulting in extensive side reactions. To see if this would be a problem in a DKR with vinyl butyrate present as acyl donor, a 10 μL/mL vinyl butyrate solution in CH_2Cl_2 was incubated with 35

TABLE 3. Changes in Optical Purity (Δee) for 4 and 7 after Racemization with Different Bases in Different Solvents at 50 °C

		Δee after 6.5 h[a] (%)	
base	solvent	ester **4**	alcohol **7**
TBD	*n*-hexane	92	18
	n-hexane with 10% MeOH	*b*	*b*
	MTBE	90	16
	H_2O[c]	0	23
	THF	88	16
	THF with 5% H_2O[c]	0	15
	2-propanol	44	19
	n-hexane with 13% 2-propanol[d]	8	4
DBU	*n*-hexane	2	2
	MTBE	0	0
	H_2O[c]	0	25
	THF	2	1
	THF with 5% H_2O[c]	0	8
	2-propanol	20	7
	n-hexane with 13% 2-propanol[d]	10	9
DBN	*n*-hexane	2	1
	MTBE	0	0
	H_2O	0	34
	THF	0	0
	2-propanol	4	0
	n-hexane with 13% 2-propanol[d]	2	1

[a] The % ee of the starting material before racemization was 99% ee (ester) and 94% ee (alcohol). The change in optical purity was monitored by GC analysis to calculate Δee values. [b] Ester completely methanolyzed. [c] Racemization performed at 37 °C. [d] Measured after 22 h.

TABLE 4. Results from Racemization of Acyloins 7 (92 % ee) and 8 (87 % ee), and Their Corresponding Esters 4 (99 % ee) and 6 (97 % ee) with Different Acidic Resins in Different Solvents

			Δee[a] after 22.5 h (%)	
substrates	solvent	resin	ester	alcohol
4 and **7**	*n*-hexane/water	Amberlyst 15	0	13
4 and **7**	*n*-hexane/water	Amberlite IR-120	0	39
4 and **7**	*n*-hexane/water	Amberlite 200	0	12
4 and **7**	*n*-hexane/water	Dowex C	0	29
6 and **8**	*n*-hexane	Amberlyst 15	0[b]	41[b]
6 and **8**	*n*-hexane	Amberlite IR-120	0[b]	26[b]
6 and **8**	*n*-hexane	Dowex C	0[b]	32[b]
6 and **8**	THF	Amberlite IR-120	0	2
6 and **8**	THF	Dowex C	0	1
6 and **8**	THF	Amberlyst 15	0	1
6 and **8**	*n*-hexane/CH_2Cl_2 (1:1)	Amberlyst 15	0	0
6 and **8**	MTBE	Amberlyst 15	0	0
6 and **8**	diethyl ether	Amberlyst 15	0	3
6 and **8**	vinyl acetate	Amberlyst 15	0	side reactions[c]

[a] The % ee of the starting material before racemization was as stated above. The change in optical purity was monitored by GC analysis to calculate Δee values. [b] Measured after 6 h. [c] Extensive side reactions with multiple products prohibited measurement of the respective enantiomeric excesses of ester and alcohol.

TABLE 5. Loss of Alcohols 7 and 8 Due to Side Reactions during Racemization with Acidic Resins

substrate	resin	solvent	alcohol loss after 7 h (%)
8	Amberlyst 15	*n*-hexane	18
	Amberlite IR-120	*n*-hexane	17
	Dowex C	*n*-hexane	21
7	Amberlyst 15	*n*-hexane	20
	Amberlite IR-120	*n*-hexane	26
	Dowex C	*n*-hexane	30
7	Amberlyst 15	*n*-hexane/H_2O	6
	Amberlite IR-120	*n*-hexane/H_2O	17
	Dowex C	*n*-hexane/H_2O	11

TABLE 6. Effect of Incubation with Amberlite IR-120 on Enzyme Activity

enzyme	*T* [°C]	remaining activity after 6 h [%]
BCL	37	26
CAL-B	50	51

mg of Amberlite IR-120 at 40 °C. After 63 h, the vinyl butyrate concentration had decreased by 23%. Side reactions were also observed during the racemization of acyloins in the presence of the acidic resins. The extents of these side reactions are shown in Table 5. **7** and **8** are quickly consumed during racemization with acidic resins in *n*-hexane. Such side reactions might be acid/base-catalyzed aldol reactions or may be due to isomerization of the acyloin (see below). In the biphasic system, the side reaction is slower, but still significant.

Alternatively, three basic resins (Amberlite IRA-900, Amberlite IRA-402, and Dowex A2) were used in *n*-hexane at 50 °C starting from enantioenriched (*R*)-**4** (98% ee) and (*S*)-**7** (90% ee). Unfortunately, after 6 h, complete hydrolysis of the ester was achieved by all three resins. Thus, a DKR with these agents is not possible.

To see if an acidic resin can be used for a one-pot DKR with a lipase, two different enzymes were incubated with Amberlite IR-120 for 6 h. The results are shown in Table 6.

It is evident from Table 6 that both lipases lost considerable activity upon incubation with the acidic resin. Although CAL-B, which is immobilized on an ion exchanger, is much more resilient than the powdered BCL form, the deactivation is significant and will prohibit high activity and stability and thus the efficiency of the DKR and the reuse of the catalyst. The mechanism of this deactivation is unknown, but it may have to do with the earlier-mentioned side reaction between the acidic resin and the acyloin. It is possible that there is a reactive byproduct or intermediate present that deactivates the enzyme or surface effects, and local pH effects influence the activity.

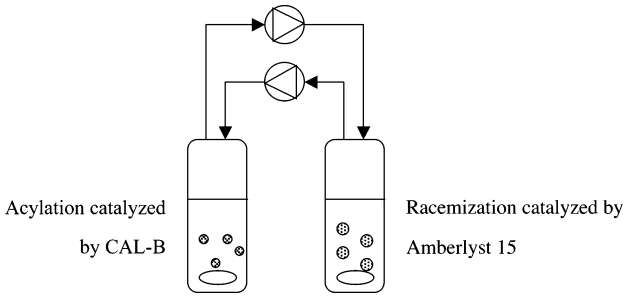
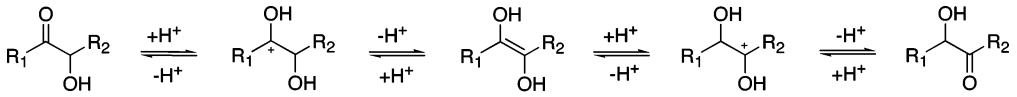


FIGURE 1. Reactor setup for a dynamic kinetic resolution of **8** with CAL-B and Amberlyst 15.

To avoid this inactivation, we designed a simple reactor setup with two 1.5 mL glass vials connected via a pump to achieve a spatial separation between the acidic resin and the enzyme (Figure 1). We investigated the DKR of the racemic acyloin (*R,S*)-**8** by transacylation with vinyl butyrate and CAL-B with Amberlyst 15 as the racemization agent in *n*-hexane. Even though CAL-B is less enantioselective than BCL in this reaction (see Table 1), it was desirable to use the immobilized enzyme to simplify retention of the catalyst in the vial. The reaction started as a kinetic resolution at 40 °C for the first 15 h, thereby reducing the initial concentration of alcohol in contact with the acidic resin. After this KR, the temperature was increased to 50 °C, and the reaction mixture was pumped continuously through both vials.

After 22 h, the resin had turned from grayish brown to dark brown−black, and the resin and enzyme were replaced by fresh material. The experiment was repeated to estimate reproducibility. Also in this run, the resin

SCHEME 4. Possible Mechanism for Acid-Catalyzed Racemization of Acyloins with the Possibility for the Formation of Isomer 9



9

had darkened after 22 h. Results from the two dynamic kinetic resolution runs are presented in Table 7.

TABLE 7. Dynamic Kinetic Resolution of 8 with Vinyl Butyrate, CAL-B, and Amberlyst 15 in *n*-Hexane[a]

	conversion (%)		selectivity[b] (%)		enantiomeric excess of ester (% ee)	
T (h)	run 1	run 2	run 1	run 2	run 1	run 2
15[c]	38	42	100	100	92	94
22[d]	80	75	88	81	95	94
30[d]	98	91	100	90	91	93

[a] Using the reactor setup shown in Figure 1. [b] Defined as the percentage of converted alcohol that is turned into ester. [c] Only KR for 15 h at 40 °C. [d] DKR at 50 °C.

It is obvious from Table 7 that a dynamic kinetic resolution of acyloins is now possible by enzymatic transesterification with vinyl butyrate combined with chemical racemization of the substrate alcohol by an acidic resin. It may seem surprising that the selectivity increases between 22 and 30 h, but this can be explained by the fact that the extent of the side reactions decreases with decreasing alcohol concentration (increased degree of conversion). It should be noted that the overall selectivity could not increase from 88 to 100% (run 1), which was attributed to a slight error in this measurement.

In conclusion, we have shown for the first time that a dynamic kinetic resolution of acyloin **8** can be simply and efficiently achieved by combining lipase-catalyzed transesterification with a racemization of the alcohol catalyzed by an acidic resin (Amberlyst 15) in a two-compartment reactor. In principle, this reaction should also work for any other type of acyloin. Conversion and selectivity were almost excellent (≥91 and ≥88%, respectively), as was the enantiomeric purity of the product (*S*)-acyloin butyrate ester (≥91% ee).

We suggest the following mechanism for the AR-catalyzed racemization of the acyloins (Scheme 4).[3] This mechanism also explains a possible side product that might contribute to the slightly reduced selectivity, as the acyloin isomer **9** could have been formed during the racemization. However, this byproduct is not yet identified.

Experimental Section

Racemic acyloin esters were synthesized and characterized as described previously.[9,10] Racemic acyloins were obtained by saponification of the corresponding acyloin ester.[9,10] Enzymatic hydrolysis of acyloin esters was performed as reported previously.[9,10] BCL (Amano PS) and CAL-B (Chirazyme L-2, c.-f., C2), as well as all resins, were from commercial suppliers.

Analytical Methods. Acyloins and their respective esters were analyzed by chiral gas chromatography on a Shimadzu GC-14A with a Hydrodex-β-3P column and a FID detector. Yields were determined with an internal standard (cyclohexanone when determining **4** and **7**, and 4-methyl acetophenone when determining **5**, **6**, and **8**). Determination of enzyme activity was performed by incubating with 1 mM *p*-nitrophenyl acetate at pH 7.5 (50 mM sodium phosphate buffer) and measuring the amount of formed *p*-nitrophenol at 410 nm on a UV spectrophotometer.

Enzymatic Transesterification of Racemic Acyloins. Lipase (10 mg) and vinyl butyrate (75 μL) were added to 1 mL of acyloin (10 mg/mL) in *n*-hexane. The mixture was shaken in a thermoshaker at 50 °C and 1000 rpm. Samples were taken and analyzed directly by GC.

Enzymatic Deacylation of Racemic Acyloin Esters. Acyloin ester (1 mL,10 mg/mL) in 2-propanol or *n*-hexane/2-propanol (8:1) was shaken with 10 mg of lipase on a thermoshaker at 50 °C and 1000 rpm. Samples were taken and analyzed directly by GC.

Racemization of Acyloins and Acyloin Esters with Organic Bases. Enantioenriched acyloins and acyloin esters were prepared by enzymatic hydrolysis as described previously.[9,10] The product was dissolved in 950 μL of solvent. Base (50 μL, 5 mg/mL) in the same solvent was added, and the vials were shaken on a thermoshaker at 50 °C and 900 rpm. Samples were taken and analyzed by GC.

Racemization of Acyloins and Acyloin Esters with Acidic/Basic Resins. Enantioenriched acyloins and acyloin esters were prepared by enzymatic hydrolysis as described previously.[9,10] Racemization in biphasic systems: The enantioenriched product was dissolved in 500 μL of *n*-hexane, and added to 35 mg of resin in 500 μL of H_2O. In a monophasic system, the enantioenriched product was dissolved in 1 mL of solvent. The mixture was shaken at 50 °C and 1000 rpm on a thermoshaker. Samples were taken and analyzed by GC. Basic resins had been turned into their OH^- form by washing with NaOH and water, followed by water removal with acetone and drying with N_2.

Dynamic Kinetic Resolution of 8 in a Two-Compartment Reactor. The reactor setup is depicted in Figure 1. The reactor consisted of two 2 mL HPLC vials that were sealed with PTFE/rubber septa, thermostated with an oil bath, and stirred with magnetic stirrers. The reaction mixture was continuously pumped at 1.2 mL/min between the two vials by a peristaltic pump with Teflon PFA tubing (∅ = 0.61 mm). The tubes were connected to stainless steel needles that penetrated the septum. The vials were ventilated with similar needles to even out built-up pressure. Reaction: 1.5 mL of substrate solution with a concentration of 10 mg of acyloin/mL of *n*-hexane was stirred at 40 °C with 150 μL of vinyl butyrate and 10 mg of CAL-B. After a certain period of time, the pumps were started, and the mixture was allowed to move to the other vial, which contained 50 mg of Amberlyst 15. The temperature was increased to 50 °C. A total of 1.5 mL *n*-hexane was added to the two flasks, to compensate for the extra volume available when the connection to the Amberlyst 15 vial was opened. As solvent evaporated during the course of the reaction, *n*-hexane was added through the ventilation needles. These needles were also used for sampling.

Acknowledgment. We thank Ms. Gisela Schmidt (IPB) for synthetic support. L.A.W. is indebted to the state of Sachsen-Anhalt for support as part of an HWP-program.

JO051661N