Synthesis of Optically Active Vicinal Fluorohydrins by Lipase-Catalyzed Deracemization

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Three microbial lipases have been used to deracemize *trans*-2-fluorocycloalkanols **2** both by hydrolysis of the corresponding acetates **3** or chloroacetates **4** and by esterification of the fluorohydrins **2** using vinyl acetate and vinyl chloroacetate, respectively. *Pseudomonas cepacia* lipase was the most selective for the six- and the seven-membered-ring compounds, while the lipase from *Candida rugosa* was most useful for the eight-membered-ring compounds. Both lipases transform the (*R*)-enantiomers preferrentially. In contrast the lipase from *Candida antarctica* hydrolyzed the esters of *trans*-2-fluorocyclohexanol **2a** and esterified the fluorohydrin itself with very low enantiopreference for the (*R*)-isomers. The seven- and the eight-membered ring esters and the corresponding fluorohydrins were also transformed with low, but reverse, enantioselectivity.

Introduction

Synthesis of optically active fluorinated compounds exhibiting biological activity or useful properties with respect to new materials has found considerable attention during the past several years.[1] However, there are only a few methods of enantioselective syntheses of such compounds from achiral or racemic precursors. Until recently, asymmetric carbon−carbon bond formation of fluorinated building blocks[2] or asymmetric reduction of fluorinated carbonyl compounds[3] were two known strategies for synthesizing optically active fluorinated compounds. The only direct method of synthesis was asymmetric electrophilic fluorination using either enantiomerically pure *N*-fluoro compounds or catalytic enantiopure metal complexes in combination with Selectfluor.[4−6] Our discovery of the first efficient asymmetric introduction of fluoride anion by Lewis acid mediated ring opening of meso or racemic epoxides added another tool for chiral organofluorine chemistry.[7]

Optically active organofluorine compounds have also been prepared by enzymatic methods such as yeast reductions of fluorinated ketones, hydrogenations of activated olefinic double bonds, and deracemization or desymmetrization of fluorinated esters.[8] Enantiomerically enriched fluorinated carboxylic acids have mostly been synthesized by lipase-catalyzed hydrolysis of the corresponding esters.[9] There are also some examples of enantioselective esterifications of carboxylic acids or transesterifications of esters.[10] Optically active fluorinated alcohols have been obtained analogously. Two alternative pathways have been employed, namely hydrolysis of β-fluoroalkyl esters[11] or acylation of vicinal fluorohydrins.[12]

In connection with our ongoing research[13] on the regio- and stereochemistry of microbiological hydroxylation and the influence of fluorine atoms on the selectivity of such

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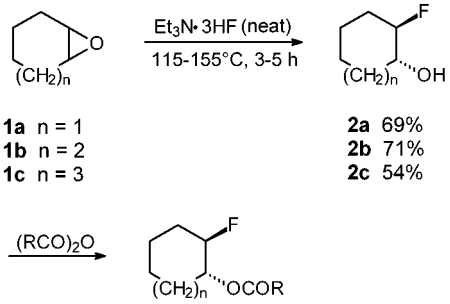
reactions, we needed both enantiomers of β-fluorocycloalkanols of ring size C_6 to C_8. Recently, we synthesized (*S*,*S*)-(+)-2-fluorocyclohexanol and (*S*,*S*)-(+)-2-fluorocycloheptanol with maximum 72% ee and 65% ee, respectively, by asymmetric ring opening of the corresponding epoxides with silver fluoride mediated by (*R*,*R*)-(−)-(salen)chromium chloride. However, almost a stoichiometric amount of the chiral Lewis acid was necessary, and the eight-membered compound was not available in this way.[7b] Herein, we present the preparation of these compounds with significantly higher enantiomeric excesses using deracemization of the corresponding esters or the acylation of the fluorohydrins in organic solvents.

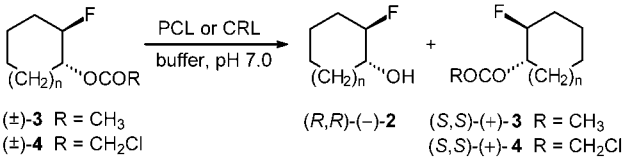
Results and Discussion

Vicinal fluorohydrins can be synthesized from epoxides by either S_N1-like or S_N2-type ring opening depending on the applied hydrofluorinating agent.[14] While reactions with HF itself or HF in combination with bases such as tetrahydrofuran or pyridine are occasionally accompanied by rearrangements,[7,15] such competing processes were not observed with less acidic, but more nucleophilic reagents such as $Et_3N{\cdot}3HF$.[16,17] We obtained the desired fluorohydrins **2** by treatment of the epoxides **1** with neat $Et_3N{\cdot}3HF$ at temperatures between 115 and 155 °C for 3−5 h. The fluorohydrins **2** were converted to the corresponding acyl compounds **3** or **4** using the respective carboxylic acid anhydrides.

Figure 1. Enantiomer preferably transferred by lipases according to the Kazlauskas rule.[19]



Having the acetates **3** or the chloroacetates **4** in hand, we investigated hydrolyses using lipases from *Pseudomonas cepacia* (PCL), *Candida antarctica* (CAL) or *Candida rugosa* (CRL). PCL and CRL have already been applied for hydrolyses of esters of *trans*-2-azidocycloalkanols or esters of *trans*-2-bromocycloalkanols.[18] In all cases, (*R*)-selectivity was observed according to Kazlauskas' rule[19] in cases when the large substituent has also the higher priority according to the CIP nomenclature (cf. Figure 1). From *C. antarctica* two isozymes A and B are produced, which differ in selectivity to a certain extent.[20] In this study, we used Novozym435, which contains the isozyme B. Using these three lipases, we hydrolyzed the corresponding racemic esters to about 50% conversion in a phosphate buffer (pH = 7.0) at room temperature. The results are shown in Table 1.



Hydrolysis of the acetates **3** took a very long time to reach 50% conversion for all enzymes. The enantioselectivity of PCL was very high for the six- and the seven-membered ring esters (E[21] > 65), yielding the (*R*,*R*)-fluorohydrins with about 90% ee and the remaining (*S*,*S*)-acetates with >92% ee. The selectivity for the eight-membered ring esters was low (Table 1, entries 1−3). For

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Table 1. Lipase-Catalyzed Hydrolysis of Acetates (±)-3 or Chloroacetates (±)-4

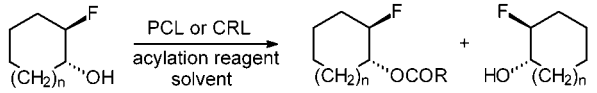
entry	acetate	lipase	time	conversion (%)	products	yield (%)	ee (%)	E^{21}
1	(±)-**3a**	PCL	4 d	53	(*S*,*S*)-(+)-**3a**	35	>95	65
					(*R*,*R*)-(−)-**2a**	29	87	66
2	(±)-**3b**	PCL	7 d	50	(*S*,*S*)-(+)-**3b**	35	92	79
					(*R*,*R*)-(−)-**2b**	43	91	67
3	(±)-**3c**	PCL	25 d	48	(*S*,*S*)-(+)-**3c**	44	26	2
					(*R*,*R*)-(−)-**2c**	43	44	4
4	(±)-**3a**	CAL	5 h	54	(*S*,*S*)-(+)-**3a**	35	66	7
					(*R*,*R*)-(−)-**2a**	47	48	5
5	(±)-**3b**	CAL	5 h	50	(*R*,*R*)-(−)-**3b**	40	6	1
					(*S*,*S*)-(+)-**2b**	37	5	1
6	(±)-**3c**	CAL	17 h	63	(*R*,*R*)-(−)-**3c**	23	66	4
					(*S*,*S*)-(+)-**2c**	44	42	5
7	(±)-**3a**	CRL	20 h	45	(*S*,*S*)-(+)-**3a**	41	80	220
					(*R*,*R*)-(−)-**2a**	40	82	20
8	(±)-**3b**	CRL	10 h	49	(*S*,*S*)-(+)-**3b**	42	78	23
					(*R*,*R*)-(−)-**2b**	41	75	15
9	(±)-**3c**	CRL	23 h	42	(*S*,*S*)-(+)-**3c**	46	71	217
					(*R*,*R*)-(−)-**2c**	39	86	25
10	(±)-**4a**	PCL	2.75 h	53	(*S*,*S*)-(+)-**4a**	35	> 95	55
					(*R*,*R*)-(−)-**2a**	29	75	18
11	(±)-**4b**	PCL	4.5 h	47	(*S*,*S*)-(+)-**4b**	41	75	27
					(*R*,*R*)-(−)-**2b**	42	73	12
12	(±)-**4c**	PCL	16 d	55	(*S*,*S*)-(+)-**4c**	30	51	4
					(*R*,*R*)-(−)-**2c**	47	28	2
13	(±)-**4a**	CAL	1.2 h	50	(*S*,*S*)-(+)-**4a**	43	< 3	1
					(*R*,*R*)-(−)-**2a**	40	< 3	1
14	(±)-**4b**	CAL	5 h	50	(*R*,*R*)-(−)-**4b**	39	21	2
					(*S*,*S*)-(+)-**2b**	37	21	2
15	(±)-**4c**	CAL	5 h	57	(*R*,*R*)-(−)-**4c**	23	47	3
					(*S*,*S*)-(+)-**2c**	44	38	4
16	(±)-**4a**	CRL	15 min	42	(*S*,*S*)-(+)-**4a**	50	28	3
					(*R*,*R*)-(−)-**2a**	34	34	3
17	(±)-**4b**	CRL	10 min	41	(*S*,*S*)-(+)-**4b**	49	34	6
					(*R*,*R*)-(−)-**2b**	33	54	5
18	(±)-**4c**	CRL	90 min	41	(*S*,*S*)-(+)-**4c**	46	50	10
					(*R*,*R*)-(−)-**2c**	42	43	3

CAL, the reaction time was shorter. However, the enantioselectivity of this enzyme was poor, particularly for the seven-membered ring (Table 1, entry 5). We find it interesting that the enantiopreference of CAL was reversed for the seven- and eight-membered ring compounds as compared with the cyclohexane derivatives (Table 1, entries 4−6 and 13−15) and compared to the reactions of the other lipases. For the hydrolysis of acetates **3** using CRL, the enantiomeric excess was reasonable for all products (Table 1, entries 7−9), while the selectivity was lower in case of the chloro acetates **4** (Table 1, entries 16−18).

As expected, hydrolysis of the corresponding chloroacetates **4** with all lipases proceeded much faster than those of the acetates. However, the enantioselectivity in most cases was much lower when compared to hydrolysis of the corresponding acetates.

Lipase-catalyzed transformations in organic solvents have recently become more common. The better solubility of most substrates in organic solvents compared to aqueous buffer systems and the easier separation of the mostly immobilized lipases favor reactions in organic media. A more facile monitoring of the reaction's progress is possible, and the isolation of the products is simpler for reactions in organic media. The polarity of organic solvents is generally less than that of aqueous buffers. Thus, the polar interactions of different parts of the protein become stronger and the enzyme becomes conformationally more rigid. Therefore, lipase-catalyzed esterifications in organic solvents or in the acylating reagent itself sometimes proceed with higher enantioselectivity as compared with the corresponding hydrolyses of the esters in a buffer system using the same enzyme.[22]

It is advantageous to use enol esters as acylating agents in general to ensure on one hand the irreversibility of the reaction, and therefore the most probable enantioselectivity, and on the other hand the enhancement of the reaction rate by using a great excess of the reagent. Thus, the fluorohydrins **2** were acylated with the above-mentioned lipases in combination with vinyl acetate or vinyl chloroacetate.



The results of acetylation of **2** with vinyl acetate by using PCL immobilized on Celite in different solvents are shown in Table 2.

With *trans*-2-fluorocyclohexanol **2a** there was not a big difference in enantioselectivity in different solvents. However, in diisopropyl ether (DIPE) or vinyl acetate itself, the highest ee was found, while the reactions in cyclohexane proceeded faster. In the case of *trans*-2-fluorocycloheptanol **2b**, the reaction in all solvents took much more time and the enantioselectivity was slightly lower. The best results were obtained in DIPE for **2a** or

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Table 2. Enantioselectivity of Acetylations of Fluorohydrins 2 with Vinyl Acetate Catalyzed by PCL Immobilized on Celite Dependent on Solvents

entry	fluorohydrin	solvent	time	conversion (%)	products	yield (%)	ee (%)	E[21]
1	(±)-**2a**	DIPE	25 h	50	(*R*,*R*)-(−)-**3a**	40	95	146
					(*S*,*S*)-(+)-**2a**	48	86	37
2	(±)-**2a**	toluene	46 h	49	(*R*,*R*)-(−)-**3a**	39	82	24
					(*S*,*S*)-(+)-**2a**	39	83	35
3	(±)-**2a**	cyclohexane	17 h	53	(*R*,*R*)-(−)-**3a**	41	86	55
					(*S*,*S*)-(+)-**2a**	33	>95	48
4	(±)-**2a**	vinyl acetate	49 h	50	(*R*,*R*)-(−)-**3a**	29	94	115
					(*S*,*S*)-(+)-**2a**	35	84	30
5	(±)-**2a**	THF	99 h	50	(*R*,*R*)-(−)-**3a**	40	75	16
					(*S*,*S*)-(+)-**2a**	31	85	33
6	(±)-**2b**	DIPE	3 d	50	(*R*,*R*)-(−)-**3b**	30	87	41
					(*S*,*S*)-(+)-**2b**	30	74	15
7	(±)-**2b**	toluene	15 d	48	(*R*,*R*)-(−)-**3b**	32	84	27
					(*S*,*S*)-(+)-**2b**	29	68	13
8	(±)-**2b**	cyclohexane	2 d	49	(*R*,*R*)-(−)-**3b**	37	84	28
					(*S*,*S*)-(+)-**2b**	48	76	19
9	(±)-**2b**	vinyl acetate	15 d	48	(*R*,*R*)-(−)-**3b**	31	86	32
					(*S*,*S*)-(+)-**2b**	39	70	15
10	(±)-**2b**	THF	16 d	49	(*R*,*R*)-(−)-**3b**	35	90	53
					(*S*,*S*)-(+)-**2b**	27	75	18
11	(±)-**2c**	DIPE	19 d	49	(*R*,*R*)-(−)-**3c**	38	24	2
					(*S*,*S*)-(+)-**2c**	36	23	2
12	(±)-**2c**	cyclohexane	42 d	32	(*R*,*R*)-(−)-**3c**	20	23	2
					(*S*,*S*)-(+)-**2c**	37	11	2
13	(±)-**2c**	vinyl acetate	56 d	31	(*R*,*R*)-(−)-**3c**	18	23	2
					(*S*,*S*)-(+)-**2c**	37	8	2

THF for **2b**, respectively (Table 2, entries 1 and 10). In contrast with the eight-membered ring fluorohydrin **2c**, only the acetylation in DIPE came to 49% conversion after 19 days, but the enantioselectivity was very poor. Only 32 or 31% conversion was found in cyclohexane or vinyl acetate after 42 or 56 days, respectively, and the enantioselectivity was also very poor (Table 2, entries 12 and 13).

The reaction time with all fluorohydrins was much shorter with vinyl chloroacetate and PCL in DIPE when compared to the corresponding reactions with vinyl acetate. The enantioselectivity was good with the six-membered and quite good with the seven-membered ring fluorohydrins. Again, the cyclooctane derivative showed an unacceptable selectivity (Table 3, entries 1−3).

Next we examined the esterifications of the fluorohydrins **2** with vinyl acetate in DIPE. Only the six-membered compound **2a** showed reasonable enantioselectivity (Table 3, entries 4−6). Interestingly, reverse stereoselection was found for the eight-membered ring fluorohydrin. With vinyl chloroacetate as the acylation reagent the reactions became very fast in DIPE. After 4−5 min, more than 50% of the fluorohydrins were converted to product. In contrast to all other esterifications, there was no enantioselectivity obtained for the esterification of **2a**, and also for the seven-membered **2b** the selectivity was quite low. Surprisingly, for the eight-membered **2c** a quite high enantiomeric excess was found for the remaining fluorohydrin (*R*,*R*)-(−)-**2c** after 55% conversion (Table 3, entry 11). The reactions became much slower in cyclohexane, while the enantioselectivity did not increase significantly for the six- and the seven-membered ring systems and, in fact, decreased for the cyclooctane derivative. For all chloroacetylations with CAL, the enantiopreference was the reverse of that obtained in the reactions catalyzed by PCL or CRL (Table 3). A similar observation was made for the transesterification of methyl mandelate using vinyl acetate and a lipase of *Pseudomonas* sp.[23]

The acetylation in pure vinyl acetate of all fluorohydrins **2** was very slow. Vinyl chloroacetate, when used as the acylation reagent, produced faster reactions. In contrast to the esterifications with PCL or CAL, the enantioselectivity was almost independent of the ring size and the acylation reagent.

Determination of the Absolute Configuration. According to the Kazlauskas rule[19] for the enantiopreference of *P. cepacia* lipase (PCL) and several other lipases of this type such as CRL, the enantiomer of **3** shown in Figure 1 should be transferred preferably. Thus, because the CHF group is larger than a CH_2 group, the (*R*,*R*)-enantiomers of acetates **3** should be hydrolyzed faster than the (*S*,*S*)-enantiomers.

To prove whether polar interactions such as hydrogen bonding of the protein to the F atom of the C−F-bond, which seems to be responsible for the modification of the biological activity of fluorinated compounds as compared to their nonfluorinated parent compounds,[24] do contradict the geometry-based rule, we determined the absolute configuration of some representative products by CD spectroscopy.[25] CD spectra of approximately 5×10^{-3} M solutions were measured in acetonitrile of the acetates

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Table 3. Acylations of Fluorohydrins 2 with Lipases Immobilized on Celite 577 (PCL and CAL) or on Lactose (CRL)

entry	fluorohydrin	solvent	lipase	acylation reagent	time	conversion (%)	products	yield (%)	ee (%)	E^{21}
1	(±)-**2a**	DIPE	PCL	vinyl chloroacetate	90 min	45	(*R*,*R*)-(−)-**4a**	43	91	47
							(*S*,*S*)-(+)-**2a**	39	81	500
2	(±)-**2b**	DIPE	PCL	vinyl chloroacetate	135 min	45	(*R*,*R*)-(−)-**4b**	44	67	9
							(*S*,*S*)-(+)-**2b**	38	75	52
3	(±)-**2c**	DIPE	PCL	vinyl chloroacetate	330 min	52	(*R*,*R*)-(−)-**4c**	39	18	2
							(*S*,*S*)-(+)-**2c**	41	21	2
4	(±)-**2a**	DIPE	CAL	vinyl acetate	2 h	50	(*R*,*R*)-(−)-**3a**	44	73	14
							(*S*,*S*)-(+)-**2a**	41	65	9
5	(±)-**2b**	DIPE	CAL	vinyl acetate	3 h	47	(*R*,*R*)-(−)-**3b**	42	46	4
							(*S*,*S*)-(+)-**2b**	40	40	4
6	(±)-**2c**	DIPE	CAL	vinyl acetate	12 h	50	(*S*,*S*)-(+)-**3c**	40	30	2
							(*R*,*R*)-(−)-**2c**	42	29	4
7	(±)-**2a**	DIPE	CAL	vinyl chloroacetate	4 min	54	4a	47	<1	1
							2a	35	<1	1
8	(±)-**2a**	cyclohexane	CAL	vinyl chloroacetate	70 min	52	(*S*,*S*)-(+)-**4a**	52	6	1
							(*R*,*R*)-(−)-**2a**	43	6	1
9	(±)-**2b**	DIPE	CAL	vinyl chloroacetate	5 min	55	(*S*,*S*)-(+)-**4b**	51	31	3
							(*R*,*R*)-(−)-**2b**	42	38	3
10	(±)-**2b**	cyclohexane	CAL	vinyl chloroacetate	180 min	46	(*S*,*S*)-(+)-**4b**	35	35	3
							(*R*,*R*)-(−)-**2b**	48	38	4
11	(±)-**2c**	DIPE	CAL	vinyl chloroacetate	5 min	55	(*S*,*S*)-(+)-**4c**	37	67	13
							(*R*,*R*)-(−)-**2c**	42	87	16
12	(±)-**2c**	cyclohexane	CAL	vinyl chloroacetate	14 h	56	(*S*,*S*)-(+)-**4c**	51	33	3
							(*R*,*R*)-(−)-**2c**	41	41	3
13	(±)-**2a**		CRL	vinyl acetate	35 d	43	(*R*,*R*)-(−)-**3a**	37	78	15
							(*S*,*S*)-(+)-**2a**	39	56	12
14	(±)-**2b**		CRL	vinyl acetate	36 d	42	(*R*,*R*)-(−)-**3b**	41	83	20
							(*S*,*S*)-(+)-**2b**	48	53	11
15	(±)-**2c**		CRL	vinyl acetate	15 d	21	(*R*,*R*)-(−)-**3c**	20	87	18
							(*S*,*S*)-(+)-**2c**	61	24	25
16	(±)-**2a**		CRL	vinyl chloroacetate	22 d	50	(*R*,*R*)-(−)-**4a**	42	80	22
							(*S*,*S*)-(+)-**2a**	40	60	7
17	(±)-**2b**		CRL	vinyl chloroacetate	2 d	49	(*R*,*R*)-(−)-**4b**	45	82	24
							(*S*,*S*)-(+)-**2b**	41	68	12
18	(±)-**2c**		CRL	vinyl chloroacetate	19 d	41	(*R*,*R*)-(−)-**4c**	47	86	24
							(*S*,*S*)-(+)-**2c**	36	52	12

(−)-**3a** (Table 2, entry 1, 95% ee), (−)-**3b** (Table 1, entry 2, after acetylation of (−)-**2b** with Ac_2O/pyridine, 90% ee), and (+)-**3c** (Table 3, entry 11, after hydrolysis of the chloroacetate (+)-**4c** and acetylation of the formed (+)-**2c** with Ac_2O/pyridine, 75% ee). The λ_{max} was determined at 214 nm for all acetates. The CD was positive for (−)-**3a** and (−)-**3b** and was negative for (+)-**3c** over the complete range of wavelengths. From the carboxylate sector rules[23] relevant for the acetate chromophores, an (*R*)-configuration for the acetoxy-substituted stereogenic center is predicted for (−)-**3a** and (−)-**3b**, while the (*S*)-configuration follows for (+)-**3c** on the basis of the following assumptions: the ring methylene groups are arranged preferably in a chair configuration (zigzag orientation), the OAc group is smaller than the CHFR moiety, and the H attached to C-1 and the carbonyl group both point in the same direction. Thus, the absolute configuration determined by CD spectroscopy for (−)-**3a** and (−)-**3b** obtained in the corresponding transformations with PCL is consistent with that predicted by the Kazlauskas rule.[19] In contrast, the transformation of the eight-membered ring compounds with CAL are in disagreement with the above-mentioned rule. An independent proof that the absolute configuration of (+)-**2a** was (1*S*,2*S*) was found by the X-ray structural analysis of two products produced by microbial hydroxylation of the *N*-phenylcarbamate of (+)-**2a**.[26]

Conclusion

For deracemizations of vicinal cyclic fluorohydrins of ring sizes C_6 to C_8, hydrolyses of the corresponding acetates **3** or chloroacetates **4** may be used. Among the three tested lipases PCL, CAL, and CRL, the first showed very good enantioselectivity for the six- and the seven-membered ring compounds **3a** and **3b**, while low selectivity was observed in the eight-membered ring compound **3c**. Comparing the reactions with PCL of the acetates **3** with the chloroacetates **4** the latter were hydrolyzed faster, as expected, but the reactions gave slightly lower ee values. CRL can be recommended for all ring sizes. The enantioselectivity of the hydrolysis of the acetates **3a** and **3c** is very high and slightly less so for the seven-membered acetate **3b**. The hydrolysis of the chloroacetates occurred much faster, but the ee values were small. When CAL was used as the biocatalyst, the enantioselectivity of the reaction was poor for all ring sizes, both for acetates and chloroacetates. The reverse

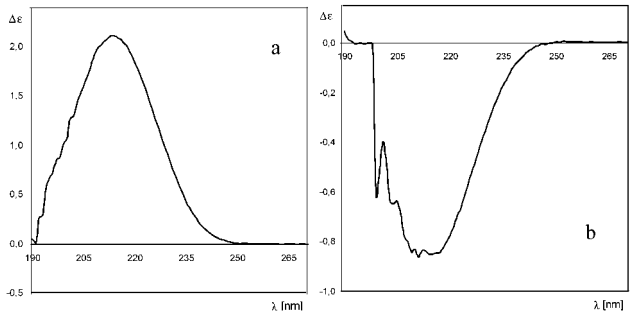

Figure 2. CD spectra of (a) (1*R*,2*R*)-(−)-1-acetoxy-2-fluorocycloheptane (**3b**), 90% ee, 6.75×10^{-3} M (corrected to 100% ee) and (b) (1*S*,2*S*)-(+)-1-acetoxy-2-fluorocyclooctane (**3c**), 75% ee, 5.6×10^{-3} M (corrected to 100% ee), each in CH_3CN at 20 °C.

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diastereoselection was obtained for the seven- and the eight-membered acetates and chloroacetates.

PCL and CRL may also be used for deracemization of fluorohydrins by acetylation or chloroacetylation in several organic solvents. Diisopropyl ether (DIPE), cyclohexane, or the acetylating reagent itself were shown to be the most suitable solvents in the case of the reactions with PCL as the immobilized biocatalyst. The highest enantioselectivity was found for the six- and the seven-membered fluorohydrins **2a** and **2b**, while this lipase did not give acceptable results for the eight-membered fluorohydrin **2c**. The acylations with PCL of **2c** were very slow both in pure vinyl acetate or vinyl chloroacetate. For CAL, the acetylations proceeded relatively fast, but the enantioselectivity was poor for all ring sizes and with both acylation reagents. Furthermore, for acetylation, the enantiopreference obtained for the six- and seven-membered ring fluorohydrin changed for the eight-membered fluorohydrin. In chloroacetylation, reverse selectivity by CAL compared to that of PCL and CRL was observed for all ring sizes.

Experimental Section

General Methods. ^{1}H NMR (300.1 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR spectra (282.3 MHz) were recorded from ca. 20% solutions in $CDCl_3$. Chemical shifts are reported as δ values (ppm) relative to TMS (^{1}H), $CDCl_3$ (^{13}C) or $CFCl_3$ (^{19}F), respectively, as internal standards. The multiplicity of ^{13}C signals was determined by the DEPT operation. Mass spectra (electron impact ionization, 70 eV) were recorded by GC/MS coupling. The conversion of substrates during enzymatic transformations was followed by GC (quartz capillary columns, 25 m × 0.33 mm, 0.52 μm HP-1 and 30 m × 0.32 mm, 0.25 μm SPB-1, temperature program, 40 → 280 °C with 10 °C/min heating rate, N_2 as the carrier gas). The ratio of compounds was determined by integration of the peak area and corrected by a factor that was determined from the ratio of peak areas of a precisely weighted mixture of the respective fluorohydrin and the corresponding acetate or chloroacetate. The products of enzymatic transformations were separated by column chromatography (silica gel, 70−230 mesh, diethyl ether/pentane 1:1). The enantiomeric excesses of the fluorohydrins and the corresponding acetates and chloroacetates were determined by chiral GC using a β-cyclodextrin column, 30m × 0.25 mm, 0.25 μm, Beta-Dex 120, isotherm 96 °C for **2a** and 111 °C for **2b** , N_2 as carrier gas. *trans*-2-Fluorocyclooctanol **2c** was silylated (0.5 mg of **2c** and two drops of *N*,*O*-bis-(trimethylsilyl)acetamide were heated to 85 °C for 2 h) prior to GC analyses (isotherm, 110 °C). The *E* value given in the tables is a measure for the selectivity of an enzyme.[21] CD spectra were determined of about 5 × 10^{-3} M solutions in acetonitrile. Optical rotations were determined at Na_D line, λ = 589 nm. Elemantal analyses were carried out by the "Mikroanalytisches Laboratorium, Organische Chemie", University of Münster.

Synthesis of 2-Fluorocycloalkanols 2, 1-Acetoxy-2-fluorocycloalkanes 3, and 1-Chloroacetoxy-2-fluoroalkanes 4. Ring Opening of Epoxides 1 with Triethylamine Trishydrogen Fluoride. In a glass vessel, the corresponding epoxide **1** (20 mmol) and $Et_3N{\cdot}3HF$ (2.38 g, 20 mmol) were stirred for 3.5 h at 115 °C (**2a**), 4 h at 155 °C (**2b**), or 5 h at 155 °C (**2c**). After being cooled at room temperature, the mixture was poured into ice−water (25 mL), neutralized with concentrated ammonia solution, and extracted with methylene chloride (2 × 20 mL). The combined organic layer was washed with saturated sodium chloride solution (20 mL) and dried over magnesium sulfate. The solvent was removed, and the residue was distilled in vacuo to yield colorless liquids.

***trans*-2-Fluorocyclohexanol 2a:** yield 1.63 g (69%); mp 23−24 °C (lit.[7] mp 22 °C). The spectroscopic data agree with those given in ref 6.

***trans*-2-Fluorocycloheptanol 2b:** yield 1.87 g (71%); bp 75 °C/0.01 bar (lit.[13a] bp 90−92 °C/25 mm). The spectroscopic data agree with those reported in ref 13a.

***trans*-2-Fluorocyclooctanol 2c:** yield 1.58 g (54%, after chromatographic separation) (lit.[27] bp 60−65 °C/2 mm); ^{1}H NMR δ 1.32−2.09 (m), 2.25 (br s, 1H), 3.78−3.89 (m, 1H), 4.46 (ddt, $^2J_{H,F}$ = 48.6 Hz, $^3J_{Ha,Ha}$ = 8.6 Hz, $^3J_{Ha,He}$ = 2.7 Hz, 1H); ^{13}C NMR δ 23.3 (t), 23.5 (t, $^2J_{C,F}$ = 7.6 Hz), 26.1 (t), 29.8 (dt, $^2J_{C,F}$ = 5.1 Hz), 30.1 (dt, $^3J_{C,F}$ = 10.2 Hz), 74.2 (dd, $^2J_{C,F}$ = 20.3 Hz), 99.2 (dd, $^1J_{C,F}$ = 162.8 Hz); ^{19}F NMR δ −182.1 (m); GC−MS *m*/*z* 146 (3), 129 (3), 128 (18), 103 (6), 100 (18), 95 (6), 83 (8), 82 (17), 81 (20), 73 (4), 72 (13), 69 (9), 67 (28), 58 (9), 57 (100).

Acetylation of Fluorohydrins 2. A solution of the fluorohydrin **2** (5 mmol), acetic anhydride (0.51 g, 5 mmol), and pyridine (0.45 g, 6 mmol) was heated at 110 °C for 3 h. After being cooled to room temperature, the mixture was dissolved in diethyl ether (15 mL) and washed with diluted HCl (3 × 5 mL) and water (5 mL). The organic layer was dried over magnesium sulfate, the solvent was evaporated, and the residue was purified by column chromatography (silica gel, pentane/diethyl ether 1:1) to give colorless liquids of the acetates **3**.

***trans*-1-Acetoxy-2-fluorocyclohexane 3a:** yield 0.73 g (91%). Spectroscopic data agree with published data.[28]

***trans*-1-Acetoxy-2-fluorocycloheptane 3b:** yield 0.81 g (93%); ^{1}H NMR δ 1.38−1.94 (m, 10H), 2.01 (s, 3H), 4.54 (dm, $^2J_{H,F}$ = 48.3 Hz), 4.90−5.02 (m, 1H); ^{13}C NMR δ 20.8 (q), 21.3 (dt, $^3J_{C,F}$ = 7.6 Hz), 22.7 (t), 27.9 (t), 29.1 (dt, $^3J_{C,F}$ = 7.6 Hz), 30.5 (dt, $^2J_{C,F}$ = 20.4 Hz), 76.5 (dd, $^2J_{C,F}$ = 33.1 Hz), 95.5 (dd, $^1J_{C,F}$ = 173.0 Hz), 169.8 (s); ^{19}F NMR δ −170.8 (m); GC−MS *m*/*z* 174 (0.2), 159 (0.1), 156 (0.4), 132 (21), 114 (30), 112 (27), 99 (10), 94 (20), 85 (8), 79 (7), 72 (9), 68 (14), 67 (8), 55 (11), 54 (4), 44 (8), 43 (100). Anal. Calcd for $C_9H_{15}FO_2$ (174.2): C, 62.06; H, 8.68. Found: C, 61.64; H, 8.96.

***trans*-1-Acetoxy-2-fluorocyclooctane 3c:** Yield 0.84 g (89%); ^{1}H NMR δ 1.33−2.00 (m, 12H), 2.04 (s, 3H), 4.53 (dm, $^2J_{H,F}$ = 48.4 Hz), 4.90−5.02 (m, 1H); ^{13}C NMR δ 21.2 (q), 23.5 (dt, $^3J_{C,F}$ = 5.1 Hz), 24.0 (t), 25.4 (t), 25.8 (t,), 28.5 (dt, $^3J_{C,F}$ = 7.6 Hz), 29.5 (dt, $^2J_{C,F}$ = 20.3 Hz), 76.2 (dd, $^2J_{C,F}$ = 22.9 Hz), 95.0 (dd, $^1J_{C,F}$ = 172.9 Hz), 170.3 (s); ^{19}F NMR δ −173.1 (m); GC−MS *m*/*z* 189 (0.2), 188 (2), 171 (0.6), 170 (5), 160 (3), 146 (32), 128 (72), 126 (52), 108 (23), 100 (90), 98 (74), 86 (20), 85 (25), 82 (57), 76 (38), 72 (36), 67 (49), 59 (22), 57 (30), 55 (48), 54 (20), 44 (34), 43 (100), 41 (66), 39 (28). Anal. Calcd for $C_{10}H_{17}FO_2$ (188.2): C, 63.81; H, 9.10. Found: C, 63.57; H, 9.38.

Chloroacetylation of Fluorohydrins 2. A solution of the fluorohydrin **2** (1 mmol) and chloroacetic anhydride (0.17 g, 1 mmol) was heated to 80 °C for 8 h. After being cooled to room temperature, the mixture was dissolved in diethyl ether (5 mL) and poured into water (8 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined ethereal phase was washed with water (5 mL) and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography (silica gel, pentane/diethyl ether 1:1).

***trans*-1-Chloroacetoxy-2-fluorocyclohexane 4a:** yield 0.17 g (85%); mp 34−37 °C; ^{1}H NMR δ 1.18−1.81 (m, 6H), 1.96−2.17 (m, 2H), 4.05 (s, 2H), 4.41 (dddd, $^2J_{H,F}$ = 50.6 Hz, $^3J_{Ha,Ha}$ = 8.4 Hz, $^3J_{Ha,Ha}$ = 10.4 Hz, $^3J_{Ha,He}$ = 4.9 Hz, 1H), 4.85−4.96 (m, 1H); ^{13}C NMR δ 22.7 (dt, $^3J_{C,F}$ = 10.2 Hz), 23.0 (t), 29.2 (dt, $^3J_{C,F}$ = 7.6 Hz), 30.4 (dt, $^2J_{C,F}$ = 17.8 Hz), 40.9 (t) 75.0 (dd, $^2J_{C,F}$ = 20.3 Hz), 91.7 (dd, $^1J_{C,F}$ = 178.0 Hz), 166.6 (s); ^{19}F NMR δ −181.7 (d, $^2J_{F,H}$ = 49.6 Hz); GC−MS *m*/*z* 176 (0.2)/174 (0.5), 145 (2), 119 (4), 118 (28), 101 (23), 100 (100), 98 (32), 85 (35), 81 (94), 80 (59), 72 (42), 59 (24), 57 (29), 55 (28), 49 (22), 41 (45). Anal. Calcd for $C_8H_{12}FClO$ (194.6): C, 49.37; H, 6.21. Found: C, 49.67; H, 6.28.

***trans*-1-Chloroacetoxy-2-fluorocycloheptane 4b:** yield 0.17 g (81%); ^{1}H NMR δ 1.40−2.02 (m, 10H), 4.04 (s, 2H), 4.41

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(dm, $^2J_{H,F}$ = 48.8 Hz), 5.00−5.10 (m, 1H); ^{13}C NMR δ 21.6 (dt, $^3J_{C,F}$ = 7.6 Hz), 22.9 (t), 28.1 (t), 29.3 (dt, $^3J_{C,F}$ = 10.2 Hz), 30.7 (dt, $^2J_{C,F}$ = 22.9 Hz), 40.9 (t) 79.6 (dd, $^2J_{C,F}$ = 22.9 Hz), 95.3 (dd, $^1J_{C,F}$ = 172.9 Hz), 166.5 (s); ^{19}F NMR δ −171.7 (m); GC−MS *m*/*z* 190 (0.5)/188 (0.9), 160 (0.5), 159 (3), 132 (46), 115 (10), 114 (100), 112 (35), 99 (36), 95 (96), 86 (38), 79 (30), 77 (84), 72 (28), 68 (54), 67 (47), 59 (18), 57 (32), 55 (53), 49 (24), 43 (19), 41 (39), 39 (13).

***trans*-1-Chloroacetoxy-2-fluorocyclooctane 4c:** yield 0.19 g (87%); ^{1}H NMR δ 1.23−2.06 (m, 12H), 4.04 (s, 2H), 4.41 (dm, $^2J_{H,F}$ = 48.3 Hz, 1H), 5.11−5.22 (m, 1H); ^{13}C NMR δ 23.4 (dt, $^3J_{C,F}$ = 7.6 Hz), 23.9 (t), 25.3 (t), 25.5 (t), 28.3 (dt, $^3J_{C,F}$ = 7.6 Hz), 29.5 (dt, $^2J_{C,F}$ = 20.4 Hz), 41.0 (t), 78.4 (dd, $^2J_{C,F}$ = 20.3 Hz), 94.6 (dd, $^1J_{C,F}$ = 170.4 Hz), 166.6 (q); ^{19}F NMR δ −173.2 (m); GC−MS *m*/*z* 222 (0.1), 207 (0.6), 174 (8), 161 (6), 146 (40), 145 (7), 129 (12), 128 (100), 109 (67), 100 (96), 95 (27), 85 (23), 82 (46), 81 (51), 77 (88), 72 (32), 67 (66).

Lipase-Catalyzed Hydrolysis of Acetates 3 or Chloroacetates 4. To a suspension of the corresponding esters **3** or **4** (1 mmol) in a phosphate buffer (30 mL, 0.1 M, pH 7.0) was added the lipase (30 mg PCL, or 80 mg CRL, or 140 mg CAL, Novozym435), and the mixture was stirred at room temperature. The conversion was followed by gas chromatography (aliquots of 0.5 mL were taken and extracted with 1 mL of diethyl ether, dried over magnesium sulfate, and analyzed). After ca. 50% of conversion, the reaction mixture was extracted with diethyl ether (3 × 15 mL). The combined ethereal extracts were dried over magnesium sulfate, and the solvent was evaporated. The remaining mixture of the acetates **3** or **4** and the corresponding fluorohydrins **2** were separated by column chromatography (silica gel, pentane/diethyl ether, 1:1), and the enantiomeric excess (chiral GC, results are given in Table 1) and the optical rotation were determined (Table 4, Supporting Information).

Immobilization of the Lipases. According to ref 29, Celite 577 (2 g) was washed with water and phosphate buffer (0.1 M, pH 7.0) and subsequently added to a suspension of PCL or CRL (0.5 g) in phosphate buffer (10 mL, 0.1 M, pH 7.0) and stirred for 30 min. The buffer was removed by filtration, and the solid was air-dried with occasionally mixing. The water content of the light brownish powder is about 1% according to ref 29. The immobilized lipases have been stored at 4 °C in a closed bottle for months without significant loss of activity.

Lipase-Catalyzed Esterifications of Fluorohydrins 2. The corresponding fluorohydrin **2** (1 mmol) and vinyl acetate or vinyl chloroacetate (2 mmol) were dissolved in the corresponding organic solvent (5 mL) or the acyl donor itself (2 mL), the immobilized lipase (74 mg PCL, 100 mg CRL, 146 mg CAL, Novozym435) was added, and the mixture was stirred at room temperature. The conversion was followed by gas chromatography (ca. 0.2 mL aliquots of the mixture were taken and filtered through silica gel prior to GC). After ca. 50% conversion of the fluorohydrin **2**, the immobilized lipase was filtered off, the solvent was evaporated, and the remaining mixture of the fluorohydrins **2** and the acetates **3** or chloroacetates **4** was separated by column chromatography. The enantiomeric excess was determined by chiral GC (the results are given in Tables 2 and 3), and the optical rotation was determined (Table 4, Supporting Information).

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Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectral data including assignments of the signals and the EI mass spectral data of the acetates **3b** and **3c** and all chloroacetates **4**, respectively. Optical rotations and the respective enantiomeric excesses of the enantiomers of **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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