Combining Lipase-Catalyzed Enantiomer-Selective Acylation with Fluorous Phase Labeling: A New Method for the Resolution of Racemic Alcohols

Benno Hungerhoff, Helmut Sonnenschein, and Fritz Theil*

ASCA GmbH Angewandte Synthesechemie Adlershof, Richard-Willstätter-Strasse 12, D-12489 Berlin, Germany

theil@asca-berlin.de.

Received July 30, 2001

Lipase-catalyzed acylation of racemic alcohols with a highly fluorinated acyl donor allows their kinetic resolution accompanied by the simultaneous enantiomer-selective fluorous phase labeling. Both the tagged and the untagged enantiomer can be separated without chromatography by a very efficient partition between a fluorous and an organic phase. The method has been successfully applied to the resolution of typically racemic secondary alcohols of low molecular weight. The fluorous label can be recovered quantitatively.

Introduction

In organic synthesis isolation of pure products is very often the bottleneck of the whole process as a result of time-consuming and waste-producing separation and purification procedures such as chromatography. In an ideal case an isolation strategy of the desired product(s) should be included in the synthetic plan.[1]

Fluorous phase techniques are excellent examples for the easy extractive recovery or isolation of homogeneous catalysts,[2] reagents, and products[3] equipped with perfluorinated auxiliary groups from nonfluorinated compounds based on partitioning between organic and fluorous phases avoiding chromatography.

Biocatalytic methods, particularly the lipase-catalyzed kinetic resolution of racemic alcohols and their esters by either esterification, hydrolysis, or alcoholysis, is a well established access to enantiomerically pure or enriched building blocks.[4] Lipases are inexpensive and robust biocatalysts; reactions are highly selective in many cases and can be run without any special equipment. However, there is one major drawback of this type of reaction yielding one of the enantiomers as an alcohol and the other one as a carboxylic ester: usually the products must be separated by chromatography, and therefore, on large scale in the pharmaceutical industry or in high-throughput kinetic resolutions, the required chromatography might be the reason lipase-catalyzed resolution is not to be regarded as useful.

To circumvent the need for chromatography, several techniques have been reported. For example, lipase-catalyzed esterification of racemic alcohols with succinic anhydride followed by an acid−base extraction separates the acidic ester from the neutral alcohol. However, acidic compounds decrease the lipase activity.[5] Transesterification of racemic esters with poly(ethylene glycol) in the presence of porcine pancreatic lipase in some cases forms crystalline poly(ethylene glycol) esters from the fast reacting enantiomer that can be simply separated from the unreacted "normal" ester by filtration.[6] On large scale, there are examples for the separation of esters from alcohols by distillation.[7] Finally, alcohols have been separated from esters by reaction with a polymeric acid chloride.[8]

From the progress made running reactions in fluorous phases and/or improving workup procedures by the introduction of the fluorous phase, the following question arises: Is it possible to combine lipase-catalyzed acylation reactions with the fluorous phase technique?

To answer this question we need a fluorinated acylating reagent that fulfills the following tasks: lipase-mediated enantiomer-selective acylation of the fast reacting enantiomer, simultaneously tagging it in order to be recognized by a fluorous phase that finally allows the separation of the fast reacting fluorinated from the nonfluorinated slow reacting enantiomer by either liquid−liquid extraction, liquid−solid extraction, or fluorous chromatography.[1b] Furthermore, it is known that fluorinated substrates[9] or solvents[10] do not harm lipases.

(1) (a) Curran, D. P. *Angew. Chem.* **1998**, *110*, 1231−1255; *Angew. Chem., Int. Ed.* **1998**, *37*, 1174−1196. (b) Curran, D. P. *Green Chem.* **2001**, G3−G7.

(2) (a) Horváth, I. T.; Rábai J. *Science* **1994**, *266*, 72−75. (b) Gladysz, J. A. *Science* **1994**, *266*, 55−56. (c) Cornils, B. *Angew. Chem.* **1997**, *109*, 2147−2149; *Angew. Chem., Int. Ed.* **1997**, *36*, 2057−2059. (d) Betzemeier, B.; Cavazini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343−4346.

(3) (a) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480−6481. (b) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 4649−4652. (c) Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667−5670.

(4) (a) Chen, C. S.; Sih, C. J. *Angew. Chem.* **1989**, *101*, 711−724; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695−707. (b) Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049−1072. (c) Faber, K.; Riva, S. *Synthesis* **1992**, 895−910. (d) Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Enzyme Microb. Technol.* **1993**, *15*, 367−382. (e) Theil, F. *Chem. Rev.* **1995**, *95*, 2203−2227. (f) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999. (g) Carrea, G.; Riva, S. *Angew. Chem.* **2000**, *112*, 2312−2341; *Angew. Chem., Int. Ed.* **2000**, *39*, 2226−2254.

(5) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; pp 44−47.

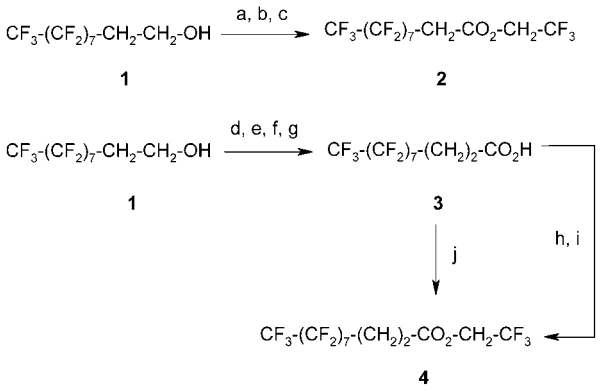
(6) (a) Wallace, J. S.; Reda, K. B.; Williams, M. E.; Morrow, C. J. *J. Org. Chem.* **1990**, *55*, 3544−3546. (b) Whalen, L. J. Morrow, C. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1279−1298.

(7) (a) Bänzinger, M.; Griffiths, G. J.; McGarrity, J. F. *Tetrahedron: Asymmetry* **1993**, *4*, 723−726. (b) Roos, J.; Stelzer, U.; Effenberger, F.; *Tetrahedron: Asymmetry* **1998**, *9*, 1043−1049.

(8) Córdova, A.; Tremblay, M. R.; Clapham, B.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 5645−5648.

10.1021/jo010767p CCC: $22.00
Published on Web 02/23/2002

Scheme 1[a]



[a] (a) Jones reagent; (b) PCl_5; (c) $HOCH_2CF_3$/pyridine; (d) TsCl; (e) LiBr; (f) Mg; (g) CO_2; (h) PCl_5; (i) $HOCH_2CF_3$/pyridine; (j) $HOCH_2CF_3$, H^+.

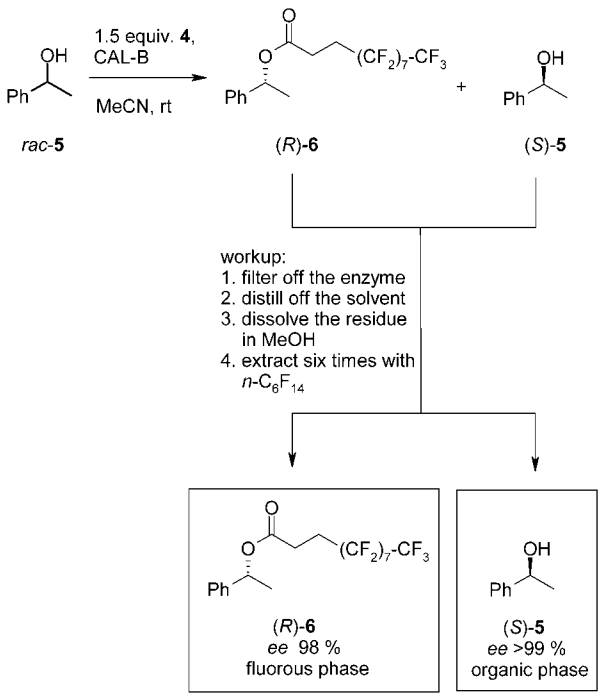
Results and Discussion

Herein we wish to report in extension and detail of our preliminary result[11] the development of a general method for the resolution of racemic alcohols by combining lipase-catalyzed enantiomer-selective acylation with fluorous phase-labeling, which complements the existing methods for the separation of esters and alcohols in lipase-catalyzed kinetic resolutions.

At first, a useful highly fluorinated acyl donor that meets all requirements regarding reactivity, stability, and fluorine content had to be designed and synthesized. From the point of reactivity, it was necessary to introduce a nonfluorinated spacer between the fluorinated alkyl and the carboxylate residue. Otherwise, acyl donors without a spacer would react nonbiocatalytically in competition to the enzyme-mediated reaction, yielding products with no or low enantiomeric excess.[12]

From the commercially available highly fluorinated decanol **1** the two esters **2** and **4** were synthesized according to Scheme 1 as potential esterification agents. First, in a three-step procedure the fluorinated ester **2**, having one methylene group as a spacer, was synthesized in analogy to a published procedure.[13] To demonstrate the feasibility of the principle, we have chosen 1-phenylethanol (*rac*-**5**) as the alcohol to be resolved into its enantiomers. Unfortunately, lipase-catalyzed acylation of *rac*-**5** with the ester **2** failed completely under variation of the lipases and reaction conditions. Neither the expected enantioselective nor the unwanted nonenantioselective acylation of *rac*-**5** with **2** was observed. On the other hand, the ester **2** seems to be a rather unstable compound that became cloudy during storage. Even when **2** was freshly distilled prior to use, no acylation was achieved. The ester **2** probably seems to eliminate hydrofluoric acid that deactivates the lipase.

Scheme 2



This observation prompted us to synthesize the homologous ester **4** via the acid **3** (Scheme 1) fitted with a CH_2-CH_2 spacer and hence having a significantly weakened ability of HF-elimination. Initially **4** was prepared via its acid chloride and reaction with 2,2,2-trifluoroethanol, but it can be prepared by direct acid-catalyzed esterification of **3** with 2,2,2-trifluoroethanol, also.

Indeed, after screening of lipases and solvents *Candida antarctica* B lipase (CAL-B) in acetonitrile turned out to be a useful biocatalyst employing 1.5 equiv of the ester **4** as an ideal acylating agent by resolving *rac*-**5** into its enantiomers (*R*)-**6** and (*S*)-**5** with high efficacy (Scheme 2).

Enantiomeric excess and yield of the products were determined after conventional workup by flash chromatography to be >99% for both enantiomers, proving that the fluorinated ester is an excellent acyl donor for lipase-catalyzed esterification. In comparison, in the literature the resolution of *rac*-**5** has been reported using vinyl acetate in *tert*-butyl methyl ether in the presence of *Pseudomonas* sp. lipase, yielding the corresponding (*R*)-acetate and the alcohol (*S*)-**5** with ee's of >99% and 93%, respectively,[14] demonstrating that the perfluoroester **4** exhibits the same enantioselectivity as vinyl acetate.

For the separation of the products we intended to use liquid−liquid extraction as a quick and simple method. Consequently, the next step was to identify a suitable fluorous/organic biphasic system for the extractive separation of the alcohol *rac*-**5** from the fluorinated ester *rac*-**6** (synthesized in a conventional nonenzymatic way from the alcohol *rac*-**5** and the corresponding acid chloride) as model substances. After screening of several biphasic systems consisting of perfluoro-*n*-hexane and various organic solvents, methanol/*n*-C_6F_{14} turned out to be the system of choice. Distribution of the products was followed in the first instance by ^1H NMR and then with

(9) (a) Hamada, H.; Shiromoto, M.; Funahashi, M.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **1996**, *61*, 2332−2336. (b) Sakai, T.; Takayama, T.; Ohkawa, T.; Oshio, O.; Ema, T.; Utaka, M. *Tetrahedron Lett.* **1997**, *38*, 1987−1990. (c) Sakai, T.; Miki, Y.; Tsuboi, M.; Takeuchi, H.; Ema, T.; Utaka, K. *J. Org. Chem.* **2000**, *65*, 2740−2747.

(10) Lemke, K.; Theil, F.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1996**, *7*, 971−974.

(11) Hungerhoff, B.; Sonnenschein, H.; Theil, F. *Angew. Chem.* **2001**, *113*, 2550−2552; *Angew. Chem., Int. Ed.* **2001**, *40*, 2492−2494.

(12) (a) Theil, F.; Schick, H.; Lapitskaya, M. A.; Pivnitsky, K. K. *Liebigs Ann. Chem.* **1991**, 195−200. (b) Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1996**, *61*, 8610−8616.

(13) Achilefu, S.; Mansuy, L.; Selve, C.; Thiebaut, S. *J. Fluorine Chem.* **1995**, *70*, 19−26.

(14) Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459−1461.

Table 1. Lipase-Catalyzed Kinetic Resolution of the Alcohols *rac*-5, *rac*-7, *rac*-9, and *rac*-11 by Acylation with the Fluorous Acyl Donor 4

		ester			alcohol					
substrate	time/h	config[c]	% ee[d]	% yield	config[c]	% ee[d]	% yield	% ester impurity	E[a]	c[b]
rac-**5**	19	*R*	98 (>99)	47	*S*	>99 (>99)	48	1	>200	0.50
rac-**7**	64	*R*	97 (99)	36	*S*	65	52	1.5	>200	0.40
rac-**9**	48	1*R*,4*S*	38 (39)	65	1*S*,4*R*	96	25	1	7.6	0.72
rac-**11**	23	1*S*,2*R*,5*S*,6*R*	96 (99)	43	1*R*,2*S*,5*R*,6*S*	>99	44	2	n.a.[e]	0.50

[a] Enantiomeric ratio. [b] Conversion. [c] Assigned on the basis of the known $[\alpha]_D$ values of the free alcohols. [d] The numbers in brackets correspond to the ee values determined after separation by flash chromatography. [e] The *E*-value calculation according to Chen and Sih[4a] is not applicable because it is a sequence of two enantioselective reactions.

higher accuracy by HPLC showing that an equimolar mixture of *rac*-**5** and *rac*-**6** in methanol required at least five extractions with perfluoro-*n*-hexane for a total separation of the fluorinated from the nonfluorinated enantiomer. The remaining organic phase was contaminated with less than 1% of *rac*-**6** and the combined fluorous phases with less than 1% of *rac*-**5**, whereby separation was carried out in ordinary separation funnels.

Having identified the appropriate biphasic solvent system, the products (*R*)-**6** and (*S*)-**5** were isolated from a lipase-mediated acylation reaction as follows (Scheme 2): removal of the enzyme by filtration, evaporation of acetonitrile, and partition between perfluoro-*n*-hexane and methanol. After extraction the organic phase contains (*S*)-**5** with 99% ee and a trace of not more than 1% of (*R*)-**6**, whereas (*R*)-**6** with an ee of 98% [determined after hydrolysis to (*R*)-**5**] and the excess of the fluoroester **4** remain in the combined fluorous phases. The ee of 98% for (*R*)-**5** represents an impurity of at most 1% of (*S*)-**5** in the fluorous phase.

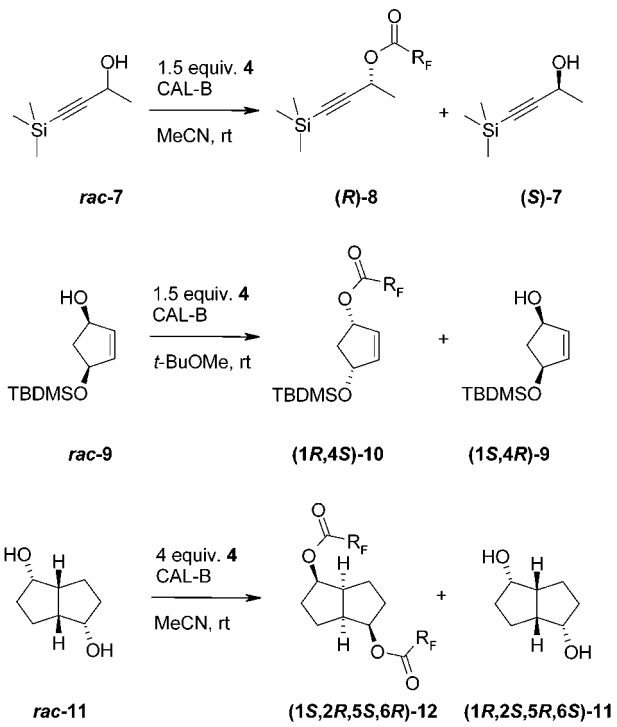
Saponification of the mixture of the fluorinated esters (*R*)-**6** and the excess of **4** yielding (*R*)-**5** with lithium hydroxide allows the almost quantitative recovery of the fluorinated carboxylic acid as its lithium salt in solid form.

To prove the general usefulness of this newly developed separation methodology, it was applied to the racemic alcohols *rac*-**7**, *rac*-**9**, and *rac*-**11** (Scheme 3). These racemic alcohols and their enantiomers, known as versatile building blocks, were resolved by utilizing the acylating agent **4** in the presence of CAL-B in acetonitrile (*rac*-**7**, *rac*-**11**) or *tert*-butyl methyl ether (*rac*-**9**) as solvents and methanol/perfluoro-*n*-hexane as the fluorous/organic biphasic system for the extractive separation of the fluorinated from the nonfluorinated enantiomer.

Independently of the constitution of the products, the extractive separation of the fluorinated from the nonfluorinated enantiomer was very efficient in all cases, demonstrating that the highly fluorinated ester **4** is an efficient acyl donor and tagging agent establishing a sufficient fluorine content in the fast reacting enantiomers.

The results summarized in Table 1 show that the newly developed separation principle could be applied successfully to substrates of different constitution that have already been resolved in the literature by lipase-catalysis using conventional nonfluorinated acyl donors and separation techniques. For example, the enantiomers of the silylated butynol *rac*-**7** have been resolved with a comparable high enantioselectivity by using vinyl acetate in the presence of *Pseudomonas* sp. lipase[15a] or with *S*-ethylthio octanoate in the presence of *Candida antarctica*

Scheme 3[a]



[a] $R_F = (CH_2)_2(CF_2)_7CF_3$.

B lipase.[15b] Furthermore, the resolution of the monosilylated cyclopentenol *rac*-**9** with isopropenyl acetate in the presence of *C. antarctica* B lipase proceeded with low enantioselectivity ($E = 15$), too, as reported by Curran et al.[16] The bicyclic C_2-symmetric diol *rac*-**11** has been resolved in our laboratory with either 2,2,2-trichloroethyl acetate in the presence of pancreatin[17a] or more efficiently with vinyl acetate in the presence of lipase from *Pseudomonas cepacia*.[17b]

The fluorine content of the faster reacting enantiomer determines the partition properties of this enantiomer between the fluorous and the organic phase. By taking the ratio of fluorine to hydrogen in the molecule as a very rough measure for the fluorophilicity of an organic compound, the ratio F/H for the esters **6**, **8**, **10**, and **12** is 1.31, 1.00, 0.68 and 1.70, respectively. The comparison

(15) (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129−6139. (b) Rotticci, D.; Orrenius, C.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1997**, *8*, 359−362.

(16) (a) Curran, T. T.; Hay, D. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2791−2792. (b) Curran, T. T.; Hay, D. A.; Koegel, C. P.; Evans, J. C. *Tetrahedron* **1997**, *53*, 1983−2004.

(17) (a) Djadchenko, M. A. Pivnitsky, K. K.; Theil, F.; Schick, H. *J. Chem. Soc., Perkin Trans.* 1 1989, 2001−2002. (b) Lemke, K.; Ballschuh, S.; Kunath, A.; Theil, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2051−2055.

of these ratios illustrates that the extractive separation is efficient even in the case when fluorine is in shortage over hydrogen as in the case of the cyclopentenol derivative **10**. In addition, the selectivity of the partition of the fluorinated esters and alcohols between perfluoro-*n*-hexane and methanol may be increased as a result of the formation of hydrogen bonds between the enantiomeric alcohols and methanol. Alternatively, for the isolation of compounds with a low fluorine content, solid−liquid extraction is a useful separation technique.[1b]

Regarding price and availability the highly fluorinated acyl donor **4** cannot compete with the frequently used inexpensive vinyl acetate but the fluorous label can be recycled. On the other hand, perfluoro-*n*-hexane, FC-72, is a technical product. Its improper use on large scale can cause environmental problems that could be avoided by using an appropriate extraction technique different from separatory funnels as typical for laboratory workup.

Conclusions

The highly fluorinated carboxylic ester **4** is an extremely useful and selective acyl donor for the lipase-catalyzed enantiomer-selective acylation of alcohols, whereby the faster reacting enantiomer is equipped with a fluorous tag in order to be recognized selectively by a fluorous phase. The enantiomer-selective labeled mixture of ester and alcohol representing the two enantiomers can be separated very efficiently by partition in the two-phase solvent system perfluoro-*n*-hexane/methanol, avoiding a chromatographic step. Hydrolysis of the fluorinated enantiomer allows the quantitative recovery of the fluorous tag.

The method accomplishes existing methods for the nonchromatographic separation of enantiomeric esters from the corresponding alcohols.

Experimental Section

All reactions, except those that were monitored by HPLC, were followed by TLC on glass plates coated with a 0.25-mm layer of silica gel. Compounds were visualized by heating with a 1% aqueous solution of $KMnO_4$ or a 1% aqueous solution of $Ce(SO_4)_2$ containing 2.5% of molybdato phosphoric acid and 6% of sulfuric acid. Analytical HPLC was carried out employing Daicel columns. Flash chromatography was performed with silica gel 60 (0.040−0.063 mm). ^{1}H NMR spectra were recorded at 300 MHz.

2*H*,2*H*-Perfluorodecanoic acid and the corresponding acid chloride were synthesized starting from commercially available 1*H*,1*H*,2*H*,2*H*-perfluoro decane-1-ol **1** (Avocado/ABCR) according to literature procedures and showed consisting spectroscopic data.[13]

2,2,2-Trifluoroethyl 2*H*,2*H*-Perfluoro Decanoate (2). To an ice-cold solution of 2*H*,2*H*-perfluoro decanoic acid chloride (20.0 g, 40.3 mmol) and 2,2,2-trifluoroethanol (4.44 g, 3.2 mL, 44.3 mmol) in dry THF (100 mL) containing a catalytic amount of DMAP (100 mg) was added dropwise over 5 min dry pyridine (3.17 g, 3.23 mL, 40.0 mmol). The cooling bath was removed, and the solution was allowed to warm to room temperature. After stirring for 1 h at room temperature, the precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the residue was partitioned between *tert*-butyl methyl ether (100 mL) and 2 N HCl (25 mL). The organic layer was washed with water (25 mL), dried (Na_2SO_4), concentrated, and distilled under reduced pressure, affording **2** (19.9 g, 88%) as a colorless liquid that crystallized at ∼6 °C. Compound **2** is moisture-sensitive and should be stored under argon at 4 °C. Prior to use, **2** was always freshly distilled by Kugelrohr distillation. Bp 58−60 °C (1×10^{-3} mbar); IR (cm^{-1}) 1809; ^{1}H NMR ($CDCl_3$) δ 3.25 (2 H, t, J = 17.1 Hz), 4.54 (2 H, q, J = 8.4 Hz).

Toluene-4-sulfonic Acid 1*H*,1*H*,2*H*,2*H*-Perfluorodecylester. To a solution of 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-ol (**1**) (400 g, 0.862 mol) and *p*-toluenesulfonyl chloride (207.0 g, 1.086 mol) in dry THF (800 mL) was added triethylamine (110.0 g, 151.3 mL, 1.086 mol) at room temperature within 10 min. The reaction mixture was refluxed under argon until **1** was completely consumed (∼10 h). The precipitate was filtered off and washed with *tert*-butyl methyl ether (500 mL). The filtrate was concentrated under reduced pressure, and the remaining residue was partitioned between a mixture of *tert*-butyl methyl ether (1000 mL), ethyl acetate (500 mL), and 2 N HCl (500 mL). The organic phase was washed with 2 N K_2CO_3 (2 × 100 mL) and brine (100 mL) and dried (Na_2SO_4). Evaporation under reduced pressure (up to 95 °C bath temperature/10 mbar) yielded the crude product still containing *p*-toluenesulfonyl chloride that was distilled off by rotatory evaporation (140−154 °C bath temperature, 0.08 mbar). The slightly brown oily residue crystallized on cooling, affording toluene-4-sulfonic acid 1*H*,1*H*,2*H*,2*H*-perfluorodecylester (470.6 g, 88%), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 2.47 (3 H, s), 2.51 (2 H, m), 4.31 (2 H, t, J = 6.9 Hz), 7.37 (2 H, d, J = 7.8 Hz), 7.81 (2 H, d, J = 7.8 Hz).

1-Bromo-1*H*,1*H*,2*H*,2*H*-perfluoro Decane. *Caution*: the bromide is a toxic lachrymator. A suspension of the above-described toluenesulfonate (470.0 g, 0.76 mol) and dry LiBr (132.0 g, 1.52 mol) in acetone (380 mL) was refluxed for 7 h and turned to a fluffy suspension. The progress of the reaction was monitored by ^{1}H NMR of an analytical sample. After complete conversion the reaction mixture was cooled to room temperature. Cyclohexane (1000 mL) was added, and the precipitate was filtered off and washed with a mixture of cyclohexane (100 mL) and acetone (20 mL) and finally with pure cyclohexane (3 × 100 mL). The filtrate was concentrated under reduced pressure, and the oily residue was distilled, affording the bromocompound (371.8 g, 93%) as a colorless liquid that crystallized at ∼6 °C. Bp 68−72 °C (0.1 mbar); ^{1}H NMR ($CDCl_3$) δ 2.70 (2 H, tt, J_1 = 8.1 Hz, J_2 = 8.4 Hz), 3.51 (2 H, t, J = 8.4 Hz). Anal. Calcd. for $C_{10}H_4BrF_{17}$ C, 23.17; H, 0.81. Found: C, 23.01; H, 0.85.

2*H*,2*H*,3*H*,3*H*-Perfluoroundecanoic Acid (3). Mg (wire, 3.16 g, 130 mmol) was heated with iodine (∼100 mg) under argon, and then dry THF (10 mL) was added after cooling. The mixture was heated to 60 °C, and the above-described bromocompound (0.53 g, 1 mmol) was added to start the Grignard reaction. Subsequently, a solution of the bromocompound (52.0 g, 98.7 mmol) in dry THF (150 mL) was slowly added within 1.25 h while keeping the reaction under gentle reflux. The mixture was refluxed for another 4 h and cooled in an ice−NaCl bath to −6 °C. Dry carbon dioxide was bubbled through the reaction mixture, whereby the temperature rose to 24 °C and a brown solid precipitated (15 min). Then, 2 N HCl (75 mL) was added slowly at 0 °C. The aqueous mixture was extracted with *tert*-butyl methyl ether (1 × 200 mL, 2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure, affording crude **3** (42.9 g, 88%) as a brown solid that was used in the next step without further purification. (If desired, **3** can be recrystallized from $CHCl_3$.) ^{1}H NMR (d_6-acetone) δ 2.57 (2 H, m), 2.69 (2 H, t, J = 8.1 Hz), 11.0 (1 H, br s).

2*H*,2*H*,3*H*,3*H*-Perfluoro Undecanoyl Chloride. A solution of **3** (43.7 g, 88.8 mmol) in dry diethyl ether (150 mL) was treated with PCl_5 (37.0 g, 177.6 mmol) and refluxed under argon (4 h). The ice-cooled reaction mixture was filtered, and the filter cake (excess PCl_5) was washed with *n*-hexane (100 mL). The filtrate was concentrated under reduced pressure, and the resulting brown oily residue was distilled under reduced pressure, affording the acid chloride (38.0 g, 84%) as a colorless liquid. Bp 95−97 °C (0.5 mbar); IR (cm^{-1}) 1800; ^{1}H NMR ($CDCl_3$) δ 2.53 (2 H, m), 3.24 (2 H t, J = 7.8 Hz).

2,2,2-Trifluoroethyl 2*H*,2*H*,3*H*,3*H*-Perfluoro Undecanoate (4). To an ice-cold solution of the above-described acid

chloride (25.5 g, 50.0 mmol) and 2,2,2-trifluoroethanol (5.2 g, 3.7 mL, 52.5 mmol) in dry THF (50 mL) containing a catalytic amount of DMAP (200 mg) was added dropwise dry pyridine (4.15 g, 4.24 mL, 52.5 mmol) over 5 min. The cooling bath was removed, and the solution was allowed to reach room temperature. After 1 h of stirring at room temperature, the precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the remaining residue was partitioned between *tert*-butyl methyl ether (100 mL) and 2 N HCl (25 mL). The organic layer was washed with water (25 mL), dried (Na_2SO_4), concentrated under reduced pressure, and distilled under reduced pressure, affording **4** (26.2 g, 91%) as a colorless liquid that crystallized at 4 °C. (Prior to use, the pH of **4** should be tested on wet pH paper after waiting for 5 min.) If necessary, traces of acid decreasing enzyme activity can be removed on large scale by simple silica gel filtration (80.0 g of **4** through a layer 4 cm in height and 13 cm in diameter with cyclohexane/ethyl acetate, 10:1). Bp 58−60 °C (1×10^{-3} mbar); ^{1}H NMR ($CDCl_3$) δ 2.51 (2 H, tt, $J_1 = 8.4$ Hz, $J_2 = 8.0$ Hz), 2.77 (2 H, t, $J = 8.4$ Hz), 4.52 (2 H, t, $J = 8.4$ Hz). Anal. Calcd for $C_{13}H_6F_{20}O_2$: C, 27.20; H, 1.05. Found: C, 27.15; H, 1.18.

An alternative procedure to get **4** directly from **3** is conducted as follows. To a solution of the acid (11.8 g, 24 mmol) in 2,2,2-trifluoro ethanol (30 mL) was added sulfuric acid (2 mL), and the mixture was refluxed for 6 h. The solvent was distilled off under reduced pressure, and the residue was partitioned between *tert*-butlyl methyl ether (60 mL) and water (20 mL). The aqueous layer was re-extracted with *tert*-butyl methyl ether (60 mL). The combined organic layers were washed with water (10 mL) and 5% aqueous $NaHCO_3$ (10 mL) and dried (Na_2SO_4). Evaporation yielded a crude liquid that was distilled by Kugelrohr distillation (oven temperature 88 °C/1×10^{-3} mbar), affording pure **4** (10.2 g, 74%). The reaction also works with the dry crude lithium salt of **3** obtained by the saponification of the mixture of (*R*)-**6** and the excess of **4**.

Kinetic Resolution of 1-Phenylethanol (*rac*-5). A solution of *rac*-**5** (1.22 g, 10 mmol) in MeCN (65 mL) was treated with the ester **4** (8.61 g, 15 mmol) and CAL-B (Chirazyme L-2, c.-f., lyo. from Boehringer Mannheim) (2.00 g). The reaction mixture was stirred at ambient temperature until the conversion reached ca. 50% (19 h). The enzyme was filtered off, and the solid residue was washed with acetone (2×40 mL). The combined filtrates were evaporated under reduced pressure, and the residue was dissolved in MeOH (25 mL). The resulting solution was extracted with *n*-C_6F_{14} (6×25 mL). The organic phase was concentrated to dryness, yielding (*S*)-**5** (0.59 g, 48%) with an ee of 99% containing ca. 1% of (*R*)-**6**. From the fluorous phase a mixture of (*R*)-**6** (ee 98%) and the excess of **4** (8.50 g) was isolated.

Saponification of (*R*)-**6** to (*R*)-**5** was carried out as follows. The mixture of (*R*)-**6** and **4** was dissolved in 1:1 mixture of THF/water (40 mL) containing LiOH (0.64 g, 26.7 mmol) and refluxed for 3 h. Subsequently, the reaction mixture was diluted with cyclohexane (100 mL), cooled to 0 °C, and filtered. The filter cake was washed with a mixture of cyclohexane (100 mL) and *tert*-butyl methyl ether (30 mL). The filtrate was concentrated to dryness, yielding (*R*)-**5** (0.57 g, 47%) with an ee of 98%. The solid filter cake (7.35 g, 98%) consists of the lithium salt of the perfluorinated carboxylic acid **3**. The enantiomeric excess was determined by HPLC on Chiralcel OJ (250 mm × 4.6 mm): mobile phase, *n*-heptane/*n*-propanol (95:5); flow rate, 1 mL/min; temperature, 22 °C; detection, UV at 254 nm. The configuration of the enantiomers was assigned by comparison with the commercially available enantiomers (*S*)- and (*R*)-**5** using chiral HPLC.

Kinetic Resolution of 1-Trimethylsilyl-1-butyne-3-ol (*rac*-7). Following the procedure for *rac*-**5** using 10 mmol of *rac*-**7** in MeCN (80 mL), CAL-B (4.00 g) and running the reaction for 64 h yielded from the organic phase (*S*)-**7** (0.74 g, 52%) with an ee of 65%. The fluorous phase contained (*R*)-**8** and the excess of **4**. The ester was cleaved as follows. The fluorous phase was evaporated under reduced pressure, and the residue was dissolved in MeOH (200 mL) containing a catalytic amount of *p*-toluenesulfonic acid (500 mg) and refluxed for 68 h. The solvent was removed under reduced pressure, and the residue was dissolved in cyclohexane/*tert*-butyl methyl ether (200:50 mL). The resulting solution was filtered and concentrated to dryness, yielding a mixture of (*R*)-**8** and methyl 2*H*,2*H*,3*H*,3*H*-perfluoro undecanoate, which were separated after dissolution in MeOH (25 mL) by extraction with *n*-C_6F_{14} (6×25 mL). From the organic phase (*R*)-**8** (0.51 g, 36%) was isolated with an ee of 97%. The enantiomeric excess was determined by HPLC on Chiralpak AD (250 mm × 4.6 mm): mobile phase, *n*-heptane/*n*-propanol (99:1); flow rate, 1 mL/min; temperature, 0 °C; detection, RI. The configuration of the enantiomeric alcohols was assigned by comparison with the reported $[\alpha]_D$ values.[15a]

Kinetic Resolution of *cis*-1-*tert*-Butyldimethylsilyloxycylopent-2-en-4-ol (*rac*-9). Following the procedure for *rac*-**5** using 10 mmol of *rac*-**9** but in *tert*-butyl methyl ether (80 mL), CAL-B (2.00 g) and running the reaction for 48 h yielded from the organic phase (1*S*,4*R*)-**9** (0.53 g, 25%) with an ee of 96%. The fluorous phase was treated as for (*R*)-**6**, yielding (1*R*,4*S*)-**9** (1.40 g, 65%) with an ee of 37%. The enantiomeric excess was determined by HPLC on Chiralcel OD (250 mm × 4.6 mm): mobile phase, *n*-heptane/*n*-propanol (99:1); flow rate, 1 mL/min; temperature, 22 °C; detection, RI. The configuration of the enantiomeric alcohols was assigned by comparison with the reported $[\alpha]_D$ values.[16b]

Kinetic Resolution of *rac-endo-endo-cis*-Bicyclo[3.3.0]-octane-2,6-diol (*rac*-11). Following the procedure for *rac*-**5** using 5 mmol of *rac*-**11** in MeCN (40 mL), **4** (11.48 g, 20 mmol), CAL-B (2.00 g), and running the reaction for 23 h yielded from the organic phase after four extractions (1*R*,2*S*,5*R*,6*S*)-**11** (0.31 g, 44%) with an ee >99% containing 1% of (1*S*,2*R*,5*S*,6*R*)-**12**. The fluorous phase was treated as for (*R*)-**6**, yielding (1*S*,2*R*,5*S*,6*R*)-**11** (0.305 g, 43%) with an ee of 96%. The enantiomeric excess was determined by HPLC on Chiralpak AD (250 mm × 4.6 mm): mobile phase, *n*-heptane/ethanol (90:10); flow rate, 1 mL/min; temperature, 22 °C; detection, RI. The configuration of the enantiomeric alcohols was assigned by comparison with the reported $[\alpha]_D$ values.[17b]

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (grant TH 562/3-1) and the Fonds der Chemischen Industrie.

JO010767P