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Synthesis of enantiopure monofluorinated phenylcyclopropanes by lipase-catalyzed kinetic resolution

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Abstract—All four stereoisomers of (2-fluoro-2-phenylcyclopropyl)methanol were synthesized using *Amano PS* lipase-catalyzed acylation and transesterification as key steps. Copper(I)-catalyzed cyclopropanation of α-fluoro styrene with ethyl diazoacetate and chromatographic separation gave diastereomerically pure cyclopropane carboxylates, which were then reduced with $LiAlH_4$. Whereas the enzymatic acylation gave low selectivities for *trans*-configured alcohols ($E=13$) using different acyl donors, the corresponding *cis*-diastereomers were obtained with high enantiomeric excesses ($E>200$). Additionally, kinetic resolution of different racemic esters of (2-fluoro-2-phenylcyclopropyl)methanol was achieved by lipase-catalyzed transesterification employing *Amano PS* in the presence of ethanol and the selectivities from this process were found to be comparable to those observed in the enzymatic acylation. The absolute configurations of the enantiomers were confirmed by X-ray structural analysis of the corresponding enantiopure *p*-bromophenyl carbamates. In addition, the stereochemistry of the product from the asymmetric cyclopropanation of α-fluoro styrene with a chiral bis(oxazoline) copper(I) catalyst was similarly determined.

1. Introduction

The cyclopropyl group is a very common structural motif in biologically active compounds and three-membered rings are frequently found in compounds applied in medicinal and agricultural chemistry.[1]

In recent years the incorporation of fluorine was identified as a powerful method for the modification of the physical properties of bioactive compounds. Whereas the replacement of a C–H group by a C–F function does not significantly alter steric demands, it often causes dramatic effects on the physiological properties.[2] This observation can be understood in terms of the specific electronic properties of this particular halogen substituent. Thus, attachment of a fluorine atom to a cyclopropane ring should exhibit a strong influence on the acidity/basicity of neighboring groups, ring-cleavage rates[3] and enzyme/substrate interactions with little change in the steric properties of the molecule.[4]

Recently, we discovered that the transition-metal-catalyzed cyclopropanation of vinyl fluorides is a powerful access racemic and enantiopure *cis*- and *trans*-2-fluoro-2-phenylcyclopropane carboxylates.[16] Phenyl substituted cyclopropanes are important intermediates in the synthesis of pharmacologically active compounds such as the anti-depressant tranylcypromine,[5] pyrethroids,[6] cysteine protease inhibitors,[7] potential anti-psychotic substances,[8] anti-HIV agents,[9] and marine lactones.[10] Since stereochemistry is important for biological activity, in most cases enantiopure derivatives were synthesized. A versatile method for the preparation of chiral building blocks is the stereochemical differentiation induced by enzymes. These biocatalysts have also been demonstrated to be very efficient for the synthesis of optically active fluorinated compounds.[11] Other authors have reported that enantiopure fluorinated cyclopropanes can be obtained using enzymatic reactions: Imura et al. produced enantiopure *cis*-2-fluorocyclopropane carboxylic acid, an intermediate in the synthesis of antibacterial quninolones, by microbial hydrolysis.[12] Optically active difluorinated cyclopropane derivatives were prepared by lipase-catalyzed deracemization[13] and desymmetrization[14] of racemic or prochiral precursors.

By analogy to their non-fluorinated counterparts we expect monofluorinated phenylcyclopropyl derivatives to be important synthetic intermediates for biologically

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active molecules. In order to obtain optically active building blocks, we examined the lipase-catalyzed acylation of *cis*- and *trans*-(2-fluoro-2-phenylcyclopropyl)methanol and the transesterification of related esters. All four stereoisomers of the latter were obtained, and absolute configurations were determined. Enol esters were found to be advantageous acylating agents, which react irreversibly and rapidly.[15]

2. Results and discussion

2.1. Synthesis of the racemic alcohols and esters

Recently, we described a procedure for the copper(I)-catalyzed cyclopropanation of vinyl fluorides with diazo acetic esters.[16] Vinyl fluorides are readily available from the corresponding alkenes by applying a two-step sequence consisting of bromofluorination with $NBS/Et_3N{\cdot}HF$[17] followed by elimination of HBr.[18] From the resulting α-fluoro styrene product **1**, the racemic esters (±)-**2** and (±)-**3** were prepared in a 1:1 ratio. The diastereomers could be separated by column chromatography on silica gel. Meyer et al. reported that only the *trans*-ester (±)-**3** could be resolved by lipase-catalyzed hydrolysis.[16] Consequently, the diastereomerically pure esters were reduced with $LiAlH_4$ to give the corresponding alcohols in excellent yields of 98% for (±)-**4** and 96% for (±)-**5** in order to apply them for deracemization (vide infra). *O*-Acylation of these racemic compounds was achieved in good yields by reaction with acetyl chloride, propionyl chloride and chloroacetic anhydride in the presence of a base (Scheme 1).

In general the configuration of diastereomeric derivatives such as (±)-**4** and (±)-**5** can be evidenced by ^1H, ^{13}C, ^{19}F, H,H COSY, and $^1H,^{19}F$ HOESY spectra. For (±)-**5** two large $^3J_{HF}$ (19.0 Hz, 19.8 Hz) are found indicating the relative *cis* configuration of fluorine to the vicinal hydrogens. In addition, $^1H,^{19}F$ HOESY spectra were recorded, which infer close spatial arrangement of the fluorine substituent to the hydrogens (Fig. 1).[19]

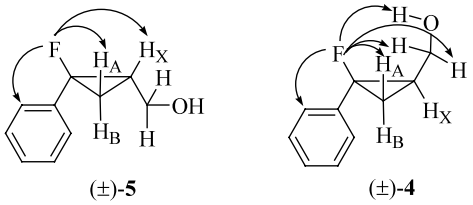


Figure 1. Fluorine–hydrogen NOEs for *cis*- and *trans*-(2-fluoro-2-phenylcyclopropyl)methanol measured by $^1H,^{19}F$ HOESY.

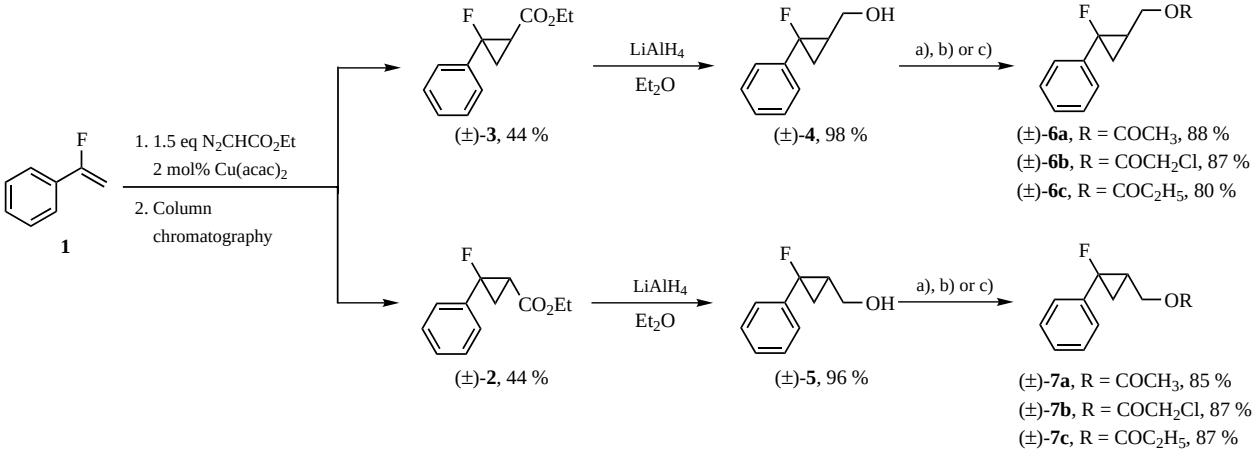
For (±)-**5** close contacts between fluorine and two hydrogens of the cyclopropane ring, the methylene proton H_A and the methine proton H_X, proved the *cis* configuration (Fig. 1). In contrast, for the *trans*-derivative (±)-**4** only the analogous NOE to the methylene proton H_A was identified. In addition, close spatial arrangement to the diastereotopic methylene protons of the CH_2OH group evidenced the *trans*-configuration. Remarkably, there was also an NOE for the fluorine substituent with the proton of the hydroxy group. This proximity might indicate the existence of a hydrogen bonding with fluorine, which would be favored by a so formed six-membered ring.

In the ^{19}F NMR spectra a very significant high field shift to −193.6 ppm (shielding effect) resulted for (±)-**4** in comparison to (±)-**5** (−159.3 ppm).

Remarkably, in the ^{13}C NMR spectra the methylene carbon of the cyclopropyl ring was shifted to higher field in case of the *cis* compound (±)-**5** (13.5 versus 17.8 ppm for (±)-**4**), whereas a $^3J_{CF}$ coupling to the CH_2OH group was only observed for the *trans* product.

2.2. Lipase-catalyzed acylation of (±)-4

Pietruszka et al. published the kinetic enzymatic resolution of *trans*-(2-phenylcyclopropyl)methanol by *Pseudomonas cepacia* lipase with low selectivity ($E=13$).[20] In a first attempt we screened several lipases and solvents



Scheme 1. *Reagents and conditions*: (a) CH_3COCl, NEt_3, Et_2O, rt, 6–7 h; (b) $(ClCH_2CO)_2O$, Py, cat. DMAP, CH_2Cl_2, rt, overnight; (c) CH_3CH_2COCl, NEt_3, Et_2O, rt, 6–7 h.

for deracemization of the analogous fluorinated alcohol (±)-**4**. Similar results to those reported for the non-fluorinated substrate were obtained using *Amano PS* lipase in toluene and *tert*-butyl methyl ether ($E=13$, Table 1, entries 1 and 2). In order to enhance the enantiomeric excess (e.e.), different vinyl esters were tested. With the sterically more demanding vinyl propionate a somewhat lower E value was observed ($E=9.3$, Table 1, entry 3). The selectivity dropped when the more reactive vinyl chloroacetate was used ($E=4.3$, Table 1, entry 4), whereas almost enantiopure (1*S*,2*S*)-**6a** was obtained using enantiomerically enriched (1*S*,2*S*)-**4** (62% e.e., Table 1, entry 5) which is available from asymmetric transition-metal-catalyzed cyclopropanation[16] after reduction. A combination of these two methods is a useful way to access enantiopure building blocks. In all cases (1*S*,2*S*)-**4** was acylated. These findings are in agreement with results observed for the non-fluorinated compound.[20]

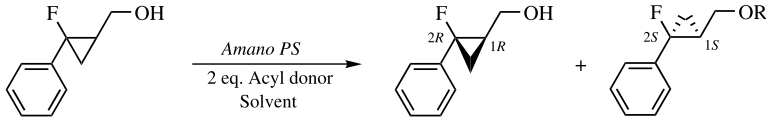
2.3. Lipase-catalyzed acylation of (±)-5

Analogous to results described in Section 2.2, the best selectivity for lipase-catalyzed deracemization of the *cis* configured alcohol (±)-**5** was achieved using lipase from *Amano PS* in *tert*-butyl methyl ether. The reactions proceeded more slowly and the selectivities increased significantly. The results were excellent for vinyl acetate and vinyl propionate ($E>200$, Table 2, entries 2 and 3). Again vinyl chloroacetate reacted faster but with lower selectivity ($E=65$, Table 2, entry 4). In all cases (1*R*,2*S*)-**5** was preferentially acylated to form the esters (1*R*,2*S*)-**7**.

2.4. Lipase-catalyzed transesterification of racemic esters

In addition to lipase-catalyzed acylation of (±)-**4** and (±)-**5**, we also became interested in the hydrolysis of esters **6** or **7** derived from the alcohols. In a first approach we tried to hydrolyze the racemic acetates (±)-**6a** and (±)-**7a** in a phosphate buffer solution in the presence of *Amano PS* lipase. In case of the *cis*-acetate (±)-**7a** no conversion was observed, for the *trans*-acetate (±)-**6a** hydrolysis occurred without selectivity. Similar results were obtained for lipases from *Candida antarctica* and *Candida rugosa*. Alternatively, lipase-mediated transesterification can be used to deracemize acylated alcohols.[11a] Therefore, we treated the racemic esters **6** or **7** with lipase *Amano PS* in *tert*-butyl methyl ether/ethanol (10:1) at 40°C. Whereas *cis* configured

Table 1. Acylation of *trans*-(±)-(2-fluoro-2-phenylcyclopropyl)methanol ((±)-**4**) with *Amano PS* lipase at rt

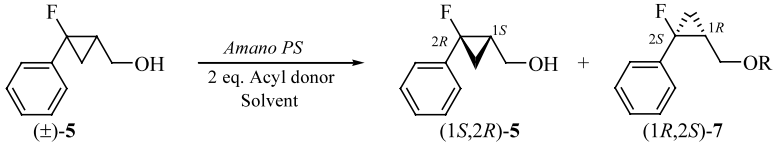


(±)-**4** (1*R*,2*R*)-**4** (1*S*,2*S*)-**6**

Entry	Solvent	Acyl donor	Time (h)	Conv. (%)	E.e. of (1*R*,2*R*)-**4**[a] (%)	E.e. of (1*S*,2*S*)-**6**[a] (%)	E[21]
1	Toluene	Vinyl acetate	7.45	50	73	73	13
2	*tert*-Butyl methyl ether	Vinyl acetate	2.5	53	79	71	13
3	*tert*-Butyl methyl ether	Vinyl propionate	2.5	53	72	63	9.3
4	*tert*-Butyl methyl ether	Vinyl chloroacetate	0.33	50	47	47	4.3
5[b]	*tert*-Butyl methyl ether	Vinyl acetate	3.75	78	18	94	n.d.

[a] Determination of absolute stereochemistry cf. Section 2.5.
[b] Enantiomerically enriched (1*S*,2*S*)-**4** (62% e.e.) was employed as starting material.

Table 2. Acylation of *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methanol (±)-**5** with *Amano PS* lipase at rt

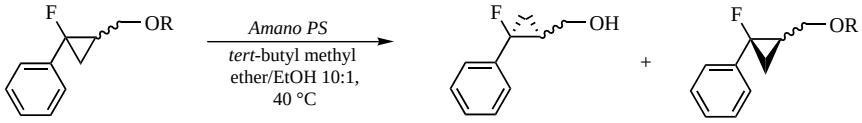


(±)-**5** (1*S*,2*R*)-**5** (1*R*,2*S*)-**7**

Entry	Solvent	Acyl donor	Time (h)	Conv. (%)	E.e. of (1*S*,2*R*)-**5**[a] (%)	E.e. of (1*R*,2*S*)-**7**[a] (%)	E[21]
1	Toluene	Vinyl acetate	7	55	71	57	7.5
2	*tert*-Butyl methyl ether	Vinyl acetate	5.25	48	90	99	>200
3	*tert*-Butyl methyl ether	Vinyl propionate	3.0	47	86	98	>200
4	*tert*-Butyl methyl ether	Vinyl chloroacetate	1.75	56	>99	80	65

[a] Determination of absolute stereochemistry cf. Section 2.5.

Table 3. Transesterification of racemic esters with *Amano PS* lipase at 40°C



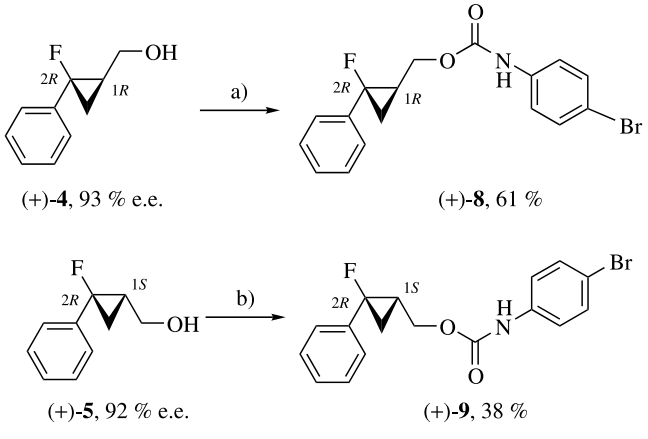
Entry	R	Ester	Time (days)	Conv. (%)	E.e. of **4** or **5** (%)	E.e. of **6** or **7** (%)	E^{21}
1	$COCH_2Cl$	(±)-**7b**	1.5	44	95 (1*R*,2*S*)-**5**	81 (1*S*,2*R*)-**7b**	97
2	$COCH_3$	(±)-**6a**	10.5	44	74 (1*S*,2*S*)-**4**	59 (1*R*,2*R*)-**6a**	12
3	COC_2H_5	(±)-**6c**	15	50	60 (1*S*,2*S*)-**4**	60 (1*R*,2*R*)-**6c**	7.2
4	$COCH_2Cl$	(±)-**6b**	0.8	55	51 (1*S*,2*S*)-**4**	60 (1*R*,2*R*)-**6b**	5.5

(±)-**7a** as well as (±)-**7c** exhibited only low conversion, the more reactive chloroacetate (±)-**7b** reacted highly selective ($E=97$, Table 3, entry 1). Reaction time was longer than for corresponding acylation accompanied with better selectivity (compare Table 2, entry 4).

As expected, the enantiomer (1*R*,2*S*)-**7b** was converted to the alcohol (1*R*,2*S*)-**5**. With identical conditions, all *trans* esters **6** were transesterificated. The acetate (±)-**6a** and the propionate (±)-**6c** reacted very slowly with selectivities comparable to those for the lipase-catalyzed acylations (Table 3, entries 2 and 3). Again, the chloroacetate (±)-**7b** reacted faster but with even lower selectivity. In all cases preferred transformation of the (1*S*,2*S*)-enantiomer to the alcohol (1*S*,2*S*)-**4** was observed.

2.5. Absolute configuration

The absolute configurations of the alcohols **4** or **5** unconverted in lipase-catalyzed acylation were determined by X-ray structural analysis of the corresponding *p*-bromophenyl carbamates (+)-**8** and (+)-**9**.[25] Synthesis of these compounds was achieved by heating enantiomerically enriched **4** (93% e.e.) and **5** (92% e.e.) with *p*-bromophenyl isocyanate in toluene or ligroine followed by recrystallization from diethyl ether/pentane (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) *p*-bromophenyl isocyanate, ligroine, Δ, 10 h, recrystallization; (b) *p*-bromophenyl isocyanate, toluene, Δ, 10 h, recrystallization.

Results of the crystallographic analysis confirmed the configurations of (+)-**8** to be (1*R*,2*R*) and of (+)-**9** to be (1*S*,2*R*) (Fig. 2). Structural details revealing close intermolecular fluorine–hydrogen contacts are discussed in Ref. 22.

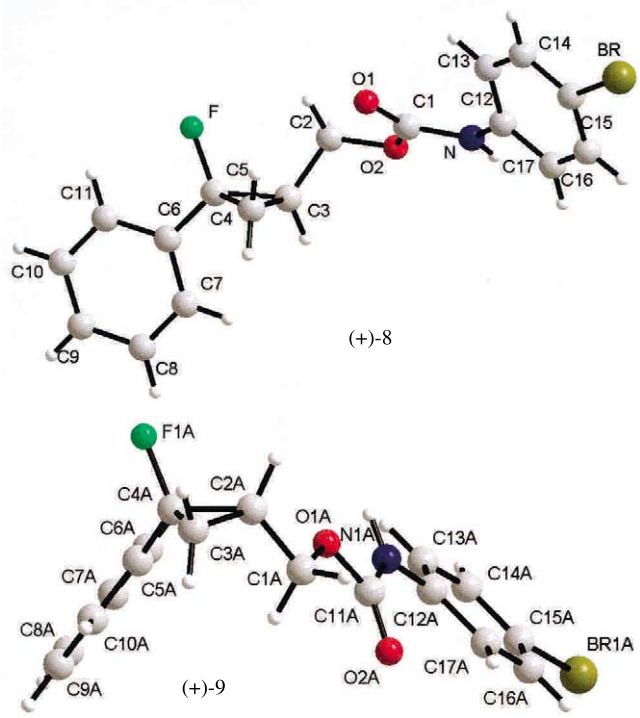
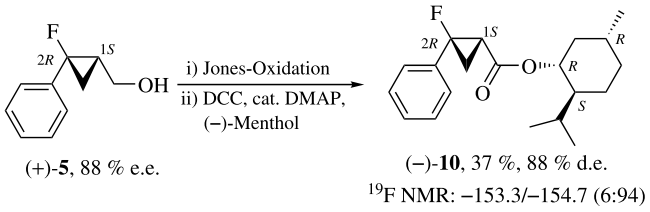


Figure 2. X-Ray structures of (1*R*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methyl-(4-bromophenyl)carbamate (+)-**8** and (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methyl-(4-bromophenyl)carbamate (+)-**9**.

As mentioned above, Meyer et al. synthesized enantiopure carboxylates by asymmetric cyclopropanation of α-fluoro styrene **1** with diazoacetates employing copper(I) 2,2-bis-[2-((4*S*)-(*tert*-butyl)-1,3-oxazolinyl)]propane complex as a catalyst.[16] The e.e. was determined by ^{19}F NMR analysis of the corresponding diastereomeric (−)-menthyl esters. Unfortunately, the absolute configuration of the formed enantioenriched *cis* esters could not be confirmed. Therefore, (+)-**5** (88% e.e.) was oxidized to the corresponding carboxylic acid using Jones' reagent. Esterification with (−)-menthol and DCC/DMAP lead to diastereomeric (−)-menthyl

esters. In the ^{19}F NMR spectra of the crude product two signals at −153.3 ppm and −154.7 were identified. Integration indicated a diastereomeric excess (d.e.) of 88% (Scheme 3).



Scheme 3.

Comparison of the chemical shifts with those reported by Meyer et al. revealed that the (1*S*,2*R*)-ester was also the enantiomer formed by asymmetric cyclopropanation. These findings are in agreement with results obtained for conversion of styrene employing the same bis(oxazoline) catalyst.[23]

3. Conclusions

In general, enzymatic methods for the preparation of enantiopure (2-fluoro-2-phenylcyclopropyl) derivatives were reported. Comparing results for the acylation of *trans*-(2-phenylcyclopropyl)methanol and its fluorinated counterpart shows that the stereopreference of the lipase of *P. cepacia* is not changed by the presence of a fluorine substituent. The nomenclature of the stereocenters, however, is reversed because of the higher priority of fluorine in the CIP system. It can also be concluded that the configuration of the stereocenter next to fluorine has an influence on enzyme–substrate recognition. For both fluorinated diastereomers, only the enantiomer with the corresponding (*S*)-configured stereogenic center next to the fluorine was converted by lipase of *Amano PS*. The importance of compounds with fluorine-containing stereogenic centers and their interaction with biomolecules has been reported already by other authors.[24] In future work we will demonstrate the utility of the synthesized monofluorinated cyclopropane derivatives in syntheses of biologically relevant molecules.

4. Experimental

4.1. Materials and methods

According to a literature procedure,[16] the *cis* and *trans* isomers of (±)-ethyl 2-fluoro-2-phenylcyclopropane carboxylate were synthesized by transition-metal-catalyzed cyclopropanation of α-fluoro styrene **1** and separation of the diastereomers by column chromatography (silica gel, pentane/diethyl ether 40:1). All reagents were obtained from commercial suppliers. Diethyl ether was dried over sodium, dichloromethane over P_2O_5. *tert*-Butyl methyl ether, vinyl acetate, vinyl chloroacetate and vinyl propionate were stored over molecular sieves (4 Å). Lipase *Amano PS* was a gift of Amano Pharmaceutical Co. Ltd., Japan. The e.e. values of alcohols were determined by gas chromatography on a HP 5890 Series II machine using a chiral Beta-Dex™ 120 stationary phase (isothermal, 135°C for (±)-**5**, 140°C for (±)-**4**). Analysis of racemic esters (±)-**6** and (±)-**7** by chiral GC did not give complete resolution of the enantiomers.

Unless otherwise stated, ^1H NMR (300.13 MHz), ^{13}C NMR (75.47 MHz), ^{19}F NMR (282.4 MHz): Bruker WM 300. For some marked cases ^1H NMR (600 MHz) and ^{19}F NMR (564.3 MHz) Varian 600 MHz apparatus Unity Plus. All spectra were recorded in $CDCl_3$ solutions. TMS was used as an internal standard for ^1H NMR, $CDCl_3$ for ^{13}C NMR and $CFCl_3$ for ^{19}F NMR spectroscopy. Mass spectra (70 eV): GC/MS coupling: Varian GC 3400/MAT 8230 and data system SS 300 of Finnigan MAT and Varian GC 3400/Varion Saturn IT (Ion Trap) and data system NIST. IR: Nicolet 5DXC-FT-IR. Melting points: DuPont Instruments 910 Differential Scanning Calorimeter with Thermal Analyst 2000, TA Instruments. Elemental analyses were performed at the microanalytical laboratory, Organic Chemistry Institute, University of Münster. Optical rotations were measured as solutions in chloroform (*c* 1.0) on a Perkin–Elmer polarimeter ($\lambda = 589$ nm) (see Tables 4 and 5). X-Ray crystal data sets were collected with Nonius CAD4 or Kappa diffractometers.

4.2. Preparation of *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methanol, (±)-5

A solution of the *cis*-isomer of (±)-ethyl 2-fluoro-2-phenylcyclopropane carboxylate ((±)-**2**) (0.78 g, 3.75 mmol) in anhydrous diethyl ether (15 mL) was slowly

Table 4. Specific rotations of *trans*-configured enantiomers prepared

Compound	Abs. config.	E.e. (%)	$[\alpha]_D^{25}$
(+)-**4**	1*R*,2*R*	98	+51.3
(−)-**4**	1*S*,2*S*	92	−50.4
(+)-**6a**	1*R*,2*R*	59	+34.1
(−)-**6a**	1*S*,2*S*	66	−36.2
(+)-**6b**	1*R*,2*R*	60	+28.4
(−)-**6b**	1*S*,2*S*	47	−22.2
(+)-**6c**	1*R*,2*R*	60	+30.2
(−)-**6c**	1*S*,2*S*	69	−35.5
(+)-**8**	1*R*,2*R*	>99	+17.4

Table 5. Specific rotations of *cis*-configured enantiomers prepared

Compound	Abs. config.	E.e. (%)	$[\alpha]_D^{25}$
(+)-**5**	1*S*,2*R*	90	+20.8
(−)-**5**	1*R*,2*S*	>99	−21.8
(−)-**7a**	1*R*,2*S*	99	−19.2
(+)-**7b**	1*S*,2*R*	81	+18.2
(−)-**7b**	1*R*,2*S*	80	−17.5
(−)-**7c**	1*R*,2*S*	97	−22.2
(+)-**9**	1*S*,2*R*	>99	+40.7

added to a suspension of $LiAlH_4$ (0.11 g, 2.8 mmol) in anhydrous diethyl ether (10 mL). The reaction mixture was heated under reflux for 2 h and then quenched with water. The resulting precipitate was dissolved by adding sulfuric acid. The aqueous phase was extracted with diethyl ether. The combined organic layer was dried (Na_2SO_4) and concentrated. (±)-**5** (0.60 g, 96%) was obtained as a colorless oil which was further purified by column chromatography (silica gel, pentane/diethyl ether 2:1). ^{1}H NMR (600 MHz):† δ 1.15 (1H, dd, J=7.1; 9.5, CH_BH$_A$), 1.48 (1H, ddd, J=7.1; 11.0; 19.0, CH_AH$_B$), 1.67 (1H, s, OH), 1.98 (1H, ddd, J=7.3; 8.3; 19.8, CH), 3.20 (1H, dd, J=8.3; 11.8, CH_2OH), 3.33 (1H, ddd, J=2.6; 7.3; 11.8, CH_2OH), 7.30–7.50 (5H, m, Ph). ^{13}C NMR: δ 13.5 (J=11.4, CH$_2$), 26.6 (J=14.0, CH), 61.2 (CH$_2$OH), 82.2 (J=213.6, C-F), 128.0 (J=5.1, Ph-CH), 128.6 (Ph-CH), 128.9 (J=3.8, Ph-CH), 134.8 (J=20.4, Ph-C). ^{19}F NMR (564.3 MHz): δ −159.3 (m). GC/MS: m/z 148 (5), 135 (100), 133 (20), 125 (45), 122 (30), 115 (52), 109 (14), 77 (7), 63 (8), 51 (9), 39 (7). IR (film): 3601, 3553–3133, 3071, 3036, 2940, 2885, 1612, 1508, 1460, 1405, 1336, 1247, 1199, 1109, 1070, 1040, 889, 813, 772, 703 cm^{-1}. Anal. calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 71.84; H, 7.17%.

4.3. Preparation of *trans*-(±)-(2-fluoro-2-phenylcyclopropyl)methanol, (±)-4

Analogous to the procedure described above, (±)-**4** (0.61 g, 98%) was synthesized using the corresponding *trans*-ester (±)-**3**. ^{1}H NMR (600 MHz):† δ 1.17–1.39 (2H, m, CH_AH$_B$), 1.60–1.71 (1H, m, CH), 1.92 (1H, s, OH), 3.80 (1H, dd, J=5.7; 11.5, CH_2OH), 4.02 (1H, dd, J=8.4; 11.5, CH_2OH), 7.24–7.35 (5H, m, Ph). ^{13}C NMR: δ 17.8 (J=12.7, CH$_2$), 28.0 (J=12.7, CH), 61.5 (J=7.6, CH$_2$OH), 81.5 (J=216.2, C-F), 124.4 (J=5.1, Ph-CH), 127.6 (Ph-CH), 128.9 (Ph-CH), 139.2 (J=20.3, Ph-C). ^{19}F NMR (564.3 MHz): δ −193.6 (m). GC/MS: m/z 166 (2), 148 (9), 136 (41), 135 (100), 133 (40), 125 (89), 122 (57), 115 (90), 109 (23), 96 (14), 77 (12), 63 (10), 51 (13), 39 (12). IR (film): 3553–3108, 3068, 3036, 2938, 2886, 1610, 1503, 1461, 1409, 1301, 1241, 1148, 1120, 1075, 1036, 892, 881, 760, 698 cm^{-1}. Anal. calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 71.82; H, 6.62%.

4.4. Preparation of *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl acetate, (±)-7a

Acetyl chloride (200 mg, 2.0 mol) in anhyd. diethyl ether (1 mL) was slowly added to an ice-cold solution of (±)-**5** (166 mg, 1 mmol) and triethyl amine (200 mg, 2.5 mmol) in anhyd. diethyl ether (5 mL). After 45 min at 0°C the solution was stirred for an additional 6–7 h at room temperature. The reaction mixture was then poured into water, and the aqueous phase was extracted with diethyl ether. The combined organic layer was dried ($MgSO_4$) and concentrated. The acetate (±)-**7a** (177 mg, 85%) was obtained after column chromatography (silica gel, cyclohexane/ethyl acetate 10:1) as a colorless oil. ^{1}H NMR: δ 1.21 (1H, ddd, J=7.4; 7.4; 9.5, CH_AH$_B$), 1.55 (1H, ddd, J=7.4; 11.2; 19.1, CH_AH$_B$), 1.97 (3H, s, CH_3), 2.00–2.10 (1H, m, CH), 3.63 (1H, dd, J=8.1; 11.9, CH_2O), 3.76 (1H, ddd, J=2.2; 7.5; 11.9, CH_2O), 7.35–7.43 (5H, m, Ph). ^{13}C NMR: δ 14.0 (J=12.7, CH$_2$), 20.6 (CH$_3$), 22.9 (J=15.2, CH), 63.3 (CH$_2$O), 82.1 (J=214.9, C-F), 128.3 (J=3.8, Ph-CH), 128.5 (Ph-CH), 129.0 (Ph-CH), 134.3 (J=20.3, Ph-C), 170.7 (CO_2CH$_3$). ^{19}F NMR: δ −159.93 (ddd, J=9.5; 19.1; 19.1). GC/MS: m/z 208 (2), 165 (2), 148 (86), 135 (15), 133 (28), 125 (11), 122 (29), 115 (21), 105 (29), 77 (8), 43 (100), 39 (5). IR (film): 2960, 1743, 1609, 1507, 1459, 1373, 1333, 1239, 1200, 1113, 1037, 998, 967, 906, 867, 768, 698, 475, 459, 445 cm^{-1}. Anal. calcd for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 68.91; H, 6.19%.

4.5. Preparation of *trans*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl acetate, (±)-6a

Analogous to the procedure described above (±)-**6a** (184 mg, 88%) was synthesized using the corresponding *trans*-alcohol (±)-**4**. ^{1}H NMR: δ 1.31–1.42 (2H, m, CH_AH$_B$), 1.62–1.74 (1H, m, CH), 2.07 (3H, s, CH_3), 4.20 (1H, ddd, J=1.2; 8.3; 11.7, CH_2O), 4.47 (1H, ddd, J=1.4; 6.5; 11.7, CH_2O), 7.24–7.38 (5H, m, Ph). ^{13}C NMR: δ 17.9 (J=12.7, CH$_2$), 20.9 (CH$_3$), 24.3 (J=11.4, CH), 62.7 (J=10.7, CH$_2$O), 80.8 (J=218.7, C-F), 124.5 (J=6.4, Ph-CH), 127.7 (Ph-CH), 128.5 (Ph-CH), 138.8 (J=20.3, Ph-C), 171.0 (CO_2CH$_3$). ^{19}F NMR: δ −192.28 (m). GC/MS: m/z 208 (1), 165 (2), 148 (100), 135 (16), 133 (33), 122 (33), 115 (22), 105 (32), 77 (9), 43 (100), 39 (6). IR (film): 1741, 1607, 1501, 1453, 1375, 1236, 1036, 758, 700, 453 cm^{-1}. Anal. calcd for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 69.09; H, 6.44%.

4.6. Preparation of *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl propionate, (±)-7c

Analogous to the procedure described for the synthesis of (±)-**7a** *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)-methyl propionate ((±)-**7c**) (180 mg, 80%) was prepared using propionyl chloride. ^{1}H NMR: δ 1.08 (3H, t, J=7.6, CH_3), 1.21 (1H, ddd, J=7.2; 7.2; 9.5 Hz, CH_AH$_B$), 1.57 (1H, ddd, J=7.2; 11.2; 19.1 Hz, 1H, CH_AH$_B$), 1.95–2.13 (1H, m, CH), 2.25 (2H, q, J=7.6, O=CCH_2), 3.61 (1H, dd, J=8.3; 11.9, CH_2O), 3.81 (1H, ddd, J=2.4; 7.4; 11.9, CH_2O), 7.33–7.47 (5H, m, Ph). ^{13}C NMR: δ 9.0 (CH$_3$), 13.9 (J=12.7, CH$_2$), 22.9 (J=15.3, CH), 27.4 (O=CCH$_2$), 63.1 (CH$_2$O), 82.0 (J=214.9, C-F), 128.3 (J=3.8, Ph-CH), 128.4 (Ph-CH), 129.2 (J=2.5, Ph-CH), 134.2 (J=20.3, Ph-C), 174.1 (CO_2CH$_2$). ^{19}F NMR: δ −160.00 (ddd, J=9.5; 19.1; 19.1). GC/MS: m/z 222 (1), 164 (3), 148 (100), 135 (9), 133 (26), 122 (25), 115 (12), 105 (26), 77 (4), 57 (59), 51 (2), 39 (2). IR (film): 3093, 3066, 3033, 2983, 2947, 2890, 1739, 1455,

† Not all ^{1}H,^{1}H-coupling constants could be determined.

1368, 1351, 1332, 1280, 1188, 1081, 1016, 993, 948, 904, 867, 811, 769, 700 cm^{-1}. Anal. calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.16; H, 6.90%.

4.7. Preparation of *trans*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl propionate, (±)-6c

Analogous to the procedure described above (±)-**6c** (196 mg, 87%) was prepared using the corresponding *trans*-alcohol (±)-**4**. ^{1}H NMR: δ 1.15 (3H, t, J=7.6, CH_3), 1.30–1.42 (2H, m, CH_AH_B), 1.62–1.74 (1H, m, CH), 2.35 (2H, q, J=7.6, O=CCH_2), 4.21 (1H, ddd, J=1.5; 8.3; 11.7, CH_2O), 4.48 (1H, ddd, J=1.4; 6.4; 11.7, CH_2O), 7.23–7.39 (5H, m, Ph). ^{13}C NMR: δ 9.0 (q, CH_3), 17.8 (J=12.7, CH$_2$), 24.3 (J=11.4, CH), 27.5 (O=CCH$_2$), 62.6 (J=8.9, CH$_2$O), 80.8 (J=218.7, C-F), 124.4 (J=6.4, Ph-CH), 127.7 (Ph-CH), 128.4 (Ph-CH), 138.8 (J=20.3, Ph-C), 174.4 (CO$_2$CH$_2$). ^{19}F NMR: δ −192.24 (m). GC/MS: m/z 222 (1), 164 (3), 148 (100), 135 (9), 133 (24), 122 (25), 115 (12), 105 (26), 77 (4), 57 (84), 51 (2), 39 (1). Anal. calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.13; H, 6.83%.

4.8. Preparation of *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl chloroacetate, (±)-7b

To a solution of (±)-**5** (166 mg, 1.00 mmol) in anhyd. dichloromethane (4 mL) chloroacetic anhydride (188 mg, 1.10 mmol), pyridine (88 mg, 1.11 mmol) and a catalytic amount 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was added. This solution was stirred overnight at room temperature and then diethyl ether (25 mL) was added. The obtained mixture was washed with 2N HCl, 5% $NaHCO_3$ and brine. The combined organic layer was dried ($MgSO_4$) and concentrated. The chloroacetate (±)-**7b** (210 mg, 87%) was obtained after column chromatography (silica gel, cyclohexane/ethyl acetate 2:1) as a colorless oil. ^{1}H NMR: δ 1.26 (1H, ddd, J=7.4; 7.4; 9.5, CH$_A$H$_B$), 1.57 (1H, ddd, J=7.4; 11.2; 19.1, CH_AH$_B$), 2.08 (1H, ddddd, J=7.4; 7.6; 8.1; 11.2; 18.6, CH), 3.74 (1H, dd, J=8.1; 11.8, CH_2O), 3.91 (1H, ddd, J=2.1; 7.6; 11.8, CH_2O), 3.97 (2H, s, CH_2Cl), 7.37–7.46 (5H, m, Ph). ^{13}C NMR: δ 14.0 (J=11.4, CH$_2$), 22.6 (J=15.3, CH), 40.6 (CH$_2$Cl), 65.1 (CH$_2$O), 82.0 (J=214.9, C-F), 128.3 (J=3.8, Ph-CH), 128.6 (Ph-CH), 129.2 (Ph-CH), 134.0 (J=20.3, Ph-C), 167.0 (CO$_2$CH$_2$Cl). ^{19}F NMR: δ −160.11 (ddd, J=9.5; 18.6; 19.1). GC/MS: m/z 148 (100), 135 (24), 133 (26), 122 (25), 115 (25), 105 (14), 77/79 (11/3). IR (film): 3092, 3064, 3033, 2959, 2898, 1758, 1504, 1454, 1413, 1366, 1336, 1311, 1289, 1254, 1188, 1032, 983, 790, 769, 702 cm^{-1}. Anal. calcd for $C_{12}H_{12}ClFO_2$: C, 59.39; H, 4.98. Found: C, 59.50; H, 5.28%.

4.9. Preparation of *trans*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl chloroacetate ((±)-6b)

Analogous to the procedure described above (±)-**6b** (210 mg, 87%) was synthesized using the corresponding *trans*-alcohol (±)-**4**. ^{1}H NMR: δ 1.35–1.46 (2H, m, CH_AH_B), 1.66–1.77 (1H, m, CH), 4.08 (2H, s, CH_2Cl), 4.34 (1H, ddd, J=1.0; 8.6; 11.7, CH_2O), 4.59 (1H, ddd, J=1.2; 6.7; 11.7, CH_2O), 7.24–7.39 (5H, m, Ph). ^{13}C NMR: δ 17.9 (J=12.7, CH$_2$), 23.8 (J=11.4, CH), 40.8 (CH$_2$Cl), 64.5 (J=10.2, CH$_2$O), 80.8 (J=220.0, C-F), 124.6 (J=6.4, Ph-CH), 128.0 (Ph-CH), 128.5 (Ph-CH), 138.4 (J=21.6, Ph-C), 167.3 (CO$_2$CH$_2$Cl). ^{19}F NMR: δ −191.32 (m). GC/MS: m/z 148 (100), 135 (23), 133 (30), 115 (24), 77/79 (12/3). IR (film): 3092, 3065, 3033, 3009, 2960, 2900, 1747, 1607, 1503, 1455, 1411, 1365, 1312, 1289, 1239, 1167, 1116, 1033, 1011, 985, 789, 758, 701 cm^{-1}. Anal. calcd for $C_{12}H_{12}ClFO_2$: C, 59.39; H, 4.98. Found: C, 59.17; H, 5.27%.

4.10. General procedure for the lipase-catalyzed acetylation of (±)-4 and (±)-5

To a solution of (±)-**4** or (±)-**5** (166 mg, 1 mmol) and the acyl donor (2 mmol) in the solvent (10 mL), lipase *Amano PS* (100 mg) was added at room temperature and stirred. The reaction was screened by GC and stopped at about 50% conversion by filtration. The organic phase was concentrated. Alcohols and esters were separated by column chromatography (silica gel, cyclohexane/ethyl acetate 10:1 to 2:1). The e.e. of the alcohol was measured by gas chromatography, as described in Section 4.1. The esters were hydrolyzed following the procedure in Section 4.11. The spectral data agree with those described for the racemic compounds.

4.11. General procedure for the hydrolysis of acetates and propionates

Potassium hydroxide (112 mg, 2 mmol) was added to a ice-cold solution of the acetate or propionate (0.24 mmol) in methanol (10 mL). After warming to room temperature the reaction mixture was stirred for 1 h. After concentration the residue was dissolved in water (5 mL) and extracted with diethyl ether. The combined organic layer was dried (Na_2SO_4) and concentrated. The e.e. of the isolated alcohol was measured by gas chromatography as described in Section 4.1.

4.12. General procedure for the lipase-catalyzed transesterification

To a stirred solution of the racemic ester (1 mmol) in *tert*-butyl methyl ether (10 mL) and ethanol (1 mL) lipase *Amano PS* (100 mg) was added at 40°C. The reaction was screened by GC and stopped at about 50% conversion by filtration. The organic phase was concentrated, and the alcohol and the esters were separated by column chromatography (silica gel, cyclohexane/ethyl acetate 10:1 to 2:1). The e.e. of the alcohol was measured by gas chromatography as described in Section 4.1. The esters were hydrolyzed following the procedure described in Section 4.11. The spectral data correspond to those described for the racemic compounds.

4.13. Absolute configuration of (+)-5

Enantiomerically enriched (+)-**5** (80 mg, 0.48 mmol, 92% e.e.) was dissolved in a small amount of toluene and added to 4-bromophenyl isocyanate (96 mg, 0.49 mmol) in toluene (10 mL). The reaction mixture was

heated under reflux for 10 h and then concentrated. Recrystallization of the white solid from diethyl ether/pentane (1:1) at −20°C afforded (+)-**9** (66 mg, 38%) as white needles (mp 112°C, $[\alpha]_D^{25}=+40.7$). One of the single crystals of (+)-**9** was used for X-ray analysis.[22,25] ^{1}H NMR: δ 1.17–1.34 (1H, m, CH_AH$_B$), 1.57 (1H, ddd, $J=7.4$; 11.2; 19.1, CH$_A$$H_B$), 1.99–2.17 (1H, m, C$H$), 3.73 (1H, dd, $J=8.0$; 11.7, CH_2O), 3.87 (1H, dd, $J=7.6$; 11.7, CH_2O), 6.57 (1H, s, NH), 7.18–7.46 (9H, m, Ph). ^{13}C NMR: δ 14.0 ($J=11.0$, CH$_2$), 23.2 ($J=16.5$, CH), 64.3 (CH$_2$O), 82.0 ($J=214.9$, C-F), 116.1 (Ph-C-Br), 120.3 (Ph-CH), 128.2 ($J=3.8$, Ph-CH), 128.6 (Ph-CH), 128.5 ($J=2.5$, Ph-CH), 132.0 (Ph-CH), 134.2 ($J=20.3$, Ph-C), 136.8 (Ph-C-N), 153.1 (O-C(O)-NH). ^{19}F NMR: δ −160.06 (m). GC/MS: m/z 365/363 (5/5), 280/278 (4/3), 217/215 (2/4), 199/197 (98/100), 169/171 (35/20), 149 (73), 148 (82), 135 (7), 129 (44), 125 (44), 122 (30), 115 (36), 109 (19), 105 (13), 90 (43), 63 (22), 51 (9), 39 (9). Anal. calcd for $C_{17}H_{15}BrFNO_2$: C, 56.06; H, 4.15; N, 3.85. Found: C, 56.13; H, 3.91; N, 4.03%.

4.14. Absolute configuration of (+)-4

In analogy to the procedure described above, (+)-**8** was synthesized using enantiomerically enriched (+)-**4** (93% e.e.) and ligroine as solvent. Recrystallization of the white solid from diethyl ether/pentane (2:1) at −20°C afforded (+)-**8** (75 mg, 61%) as white needles (mp 105°C, $[\alpha]_D^{25}=+17.4$). One of the single crystals of (+)-**8** was used for X-ray analysis.[22,25] ^{1}H NMR: δ 1.26–1.46 (2H, m, C$H_A$$H_B$), 1.67–1.80 (1H, m, C$H$), 4.21–4.28 (1H, m, C$H_2$O), 4.63 (1H, dd, $J=6.2$; 11.5 Hz, CH_2O), 6.69 (1H, s, NH), 7.24–7.40 (9H, m, Ph). ^{13}C NMR: δ 18.0 ($J=12.7$, CH$_2$), 24.5 ($J=11.4$, CH), 63.8 ($J=8.9$, CH$_2$O), 80.9 ($J=218.7$, C-F), 116.0 (Ph-C-Br), 120.3 (Ph-CH), 124.4 ($J=4.5$, Ph-CH), 127.8 (Ph-CH), 128.5 (Ph-CH), 132.0 (Ph-CH), 137.0 (Ph-C-N), 138.7 ($J=20.3$, Ph-C), 153.3 (O-C(O)-NH). ^{19}F NMR: δ −192.38 (m), GC/MS: m/z 365/363 (5/5), 280/278 (4/5), 217/215 (2/3), 199/197 (100/100), 169/171 (30/38), 149 (90), 148 (100), 135 (83), 129 (62), 125 (40), 115 (43), 99 (22), 90 (43), 63 (27), 51 (13). Anal. calcd for $C_{17}H_{15}BrFNO_2$: C, 56.06; H, 4.15; N, 3.85. Found: C, 55.93; H, 3.88; N, 3.68%.

4.15. Synthesis of (−)-menthyl (1*S*,2*R*)-2-fluoro-2-phenylcyclopropane carboxylate, (−)-10

The enantiomerically enriched alcohol (+)-**5** (283 mg, 1.71 mmol, 88% e.e.) was dissolved in acetone (8 mL). To the stirred ice-cold solution, Jones' reagent (1 mL, 2N) was added dropwise. After 15 min the solution was warmed to room temperature and further Jones' reagent was added (0.5 mL). After 6 h, the reaction was quenched with 2-propanol (1 mL). After stirring for 1 h, the solution was decanted and concentrated. The obtained residue was dissolved in satd Na_2CO_3 solution. After extraction with dichloromethane, the aqueous phase was adjusted to pH 1 with conc. HCl and extracted further with dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in anhyd. dichloromethane (20 mL) without further purification. *N*,*N*-Dicyclohexyl carbodiimide (DCC) (387 mg, 1.88 mmol), (−)-menthol (800 mg, 5.12 mmol) and a catalytic amount of DMAP were added. The mixture was stirred at room temperature for 14 h. After filtration the mixture was concentrated. For the crude ester a d.e. of 88% was determined by ^{19}F NMR spectroscopy. ^{19}F NMR: δ −153.3 (6%), −154.7 (94%). After column chromatography (silica gel, cyclohexane/ethyl acetate 80:1), the (−)-menthyl ester (−)-**10** (200 mg, 37%) was obtained as a colorless oil ($[\alpha]_D^{25}=-25.9$, 88% d.e.). The spectral data agree with those reported in the literature.[16] Anal. calcd for $C_{20}H_{27}FO_2$: C, 75.44; H, 8.55. Found: C, 75.24; H, 8.53%.

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25. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 170384 and CCDC 170385. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).