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Synthesis of optically active 2-fluoroalk-1-en-3-yl esters and chirality transfer in their Claisen-type rearrangements

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Dedicated to Professor Kenji Uneyama with best wishes on the occasion of his 65th birthday.

Abstract

A series of enantioenriched long chain 2-fluoroalk-1-en-3-ols **1** has been prepared by lipase-catalyzed resolution of the racemic compounds synthesized from terminal alkenes. The lipase of *Candida antarctica* was shown to be the most efficient one in terms of enantioselectivity. Transesterification of the fluorinated allylic alcohols **1** was superior over the hydrolysis in a phosphate buffer of the corresponding acetates **2**. Lipase-catalyzed acetylation of allylic alcohols **1** in organic medium gave (*S*)-(−)-3-acetoxy-2-fluoroalk-1-enes of chain lengths C_{10}, C_{16} and C_{18} with 68–89% yield and 92–96% ee, while the remaining (*R*)-(+)-2-fluoroalk-1-en-3-ols were isolated with 54–96% yield and 72–86% ee. The absolute configuration was assigned by comparison of measured and calculated CD-spectra, and unambiguously by ^{1}H and ^{19}F NMR spectroscopy using a modified Mosher's method. From the optically active fluorinated allylic alcohols **1** corresponding esters **2** such as propionates, 3,3,3-trifluoropropionates and Boc-glycinates were synthesized. These compounds were rearranged to 2-substituted 4-fluoroalk-4-enecarboxylic acids **3** applying modified conditions of the [3,3]-sigmatropic Ireland-Claisen rearrangement. While a complete chirality transfer from C-3 of the allylic esters to C-2 of the carboxylic acids or 2-amino acids, respectively, occurred in rearrangements of the propionates and Boc-glycinates, racemic 2-(trifluoromethyl)alk-4-enecarboxylic acids were formed from the allylic trifluoropropionates. The configurational lability of the latter products is caused by the strongly acidic proton in α-position to the trifluoromethyl and the carboxyl groups under the basic rearrangement conditions.

Keywords: Asymmetric synthesis; Lipases; Kinetic resolution; [3,3]-Sigmatropic rearrangements; Vinyl fluorides; Fluorinated allylic esters; Fluorinated amino acids; Enantioselectivity; Chirality transfer

1. Introduction

For the synthesis of enantioenriched fluorinated compounds several methods have been developed such as enantioselective electrophilic fluorination [1,2], asymmetric nucleophilic fluorination [3,4] or construction of complex stereogenic molecules by building block methods [5–8]. Nevertheless, there is still a need for new pathways.

Recently, we reported on different variations of [3,3]-sigmatropic rearrangements of the Ireland-Claisen type using fluorinated allylic esters. Thus, the Johnson-Claisen rearrangement of 2-fluoroalk-1-en-3-ols with triethyl orthoacetate gave ethyl 4-fluoroalk-4-enoates in high yield [9]. Moreover, the Irelend-Claisen rearrangement of α-substituted acetic acid esters of the mentioned fluorinated allylic alcohols such as α-chloroacetic esters or propionic esters, led to the corresponding 2-substituted 4-fluoroalk-4-enoic acids in moderate yields [9]. The reaction was shown to work also with *N*-protected glycine esters to give 2-amino-4-fluoroalk-4-enoic acids in excellent yields in a modified Kazmaier variation [10] of the Ireland-Claisen rearrangement [11]. Furthermore, we have shown that *N*-benzoyl protected fluorinated allylic esters of alanine or phenylglycine gave the corresponding *N*-benzoyl 2-amino-4-fluoro-2-methyl(or phenyl)-alk-4-enoic acids in almost quantitative yield following the mechanism of the Steglich variant [12] of the Ireland-Claisen rearrangement [13]. Based on the latter rearrangement, we developed a protocol to synthesize 3-alkyl-4-fluoropyridines (Scheme 1) [13].

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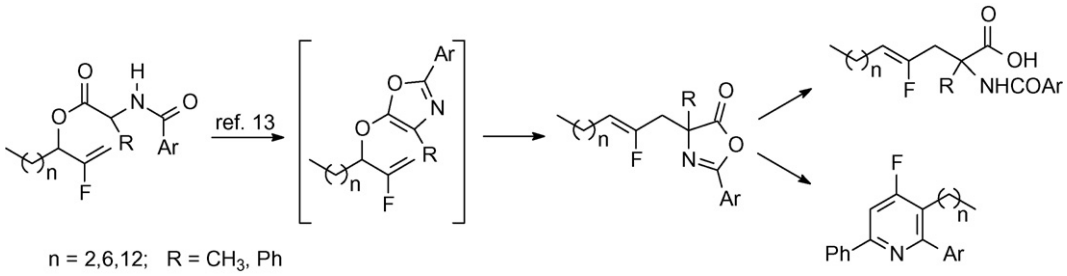


Scheme 1.

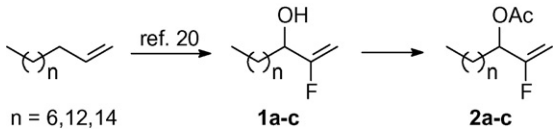
In all these reactions, the *trans*-configured double bond in 4-position was formed highly diastereoselective, due to the selective formation of *cis*-enolates in the transition state of the rearrangements. Now we were interested to investigate whether it would be possible to prepare optically active fluorinated compounds by chirality transfer from carbon-3 of the allylic esters to carbon-2 of the formed long chain 2-substituted 4-fluoroalk-4-enoic acids. This type of a chirality transfer has some precedence in similar rearrangements of non-fluorinated compounds already [14].

2. Results and discussion

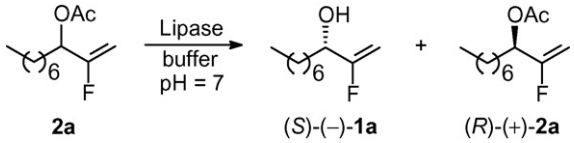
2.1. Synthesis and resolution of racemic 2-fluoroalk-1-en-3-ols and 3-acetoxy-2-fluoroalk-1-enes

According to our earlier investigations we prepared 2-fluoroalk-1-en-3-ols (**1a–c**) by bromofluorination [15,16] of terminal alkenes, subsequent HBr elimination from the formed 1-bromo-2-fluoroalkanes [17–20] and allylic hydroxylation of the resulting vinyl fluorides with substoichiometric selenium dioxide and *tert*-butylhydroperoxide in the presence of catalytic amounts of acetic acid (Scheme 2) [20].

For the preparation of optically active fluorohydrins [21], we intended kinetic resolution by lipase-catalyzed hydrolysis of the corresponding acetates **2**, which were prepared by treatment of the 2-fluoroalken-3-ols **1** with acetic anhydride or chloroacetic anhydride in the presence of pyridine. As a model compound for the resolution experiments we chose 3-acetoxy-2-fluorodec-1-ene (**2a**). Based on our earlier investigations on kinetic resolution of fluorohydrins [22–26], we tested three



Scheme 2.



Scheme 3.

different lipases, namely those from *Pseudomonas cepacia* (Amano PS), *Candida rugosa* and *Candida antarctica* (Novozym435®), to find optimal conditions for maximal enantioselectivity (Scheme 3).

The optimization reactions were performed with 2 mmol of the allylic acetate **2a**, 20 mg of the respective lipase in 60 mL of a 0.1 M phosphate buffer of pH 7.0. The results of these reactions are shown in Table 1.

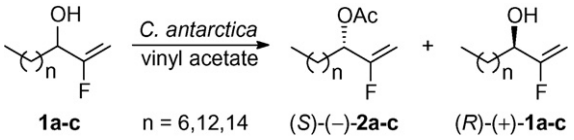
Thus, *C. antarctica* lipase was found to be the most useful enzyme in this series giving both products, the acetate (*R*)-(+)-**2a** and the remaining alcohol (*S*)-(−)-**1a**, in high enantiomeric excess after approximately 50% conversion of the starting material. However, the isolated yield of the alcohol (*S*)-(−)-**1a** was only 23%. This might be due to the poor solubility of the long-chain alcohol in water. Thus, a significant portion might be clued to the enzyme and went lost with the separated enzyme. This phenomenon has also been observed in other cases [27]. Additionally, resolution of racemates is always faced with the disadvantage of maximum 50% yield for the desired enantiomer. Thus, we tried to transform the alcohol formed by enzymatic hydrolysis of the ester, into the enantiomeric ester by Mitsunobu reaction [28]. This reaction was possible, but due to the low yield of (*S*)-(−)-**1a** in the enzymatic hydrolysis of **2a**, the yield of (*R*)-(+)-**2a** was as low as 29% and the enantiomeric excess (ee) dropped down to 74%. Consequently, we did not make any further efforts to investigate this reaction.

Instead, we subsequently concentrated on the enzymatic acylation by transesterification with vinyl acetate of the allylic alcohol and we first investigated the influence of the solvent on the enantioselectivity and the yield of the resolution (Scheme 4).

The reactions were performed using 1 mmol 2-fluorodec-1-en-3-ol (**1**), 2 mmol of vinyl acetate and 146 mg of the lipase Novozym435®. The solvents were not dried, since a small amount of water is advantageous for the reaction [29]. The results are depicted in Table 2.

Table 1
Hydrolysis of 3-acetoxy-2-fluorodec-1-ene ((*R/S*)-**2a**) with different lipases

Lipase	Conversion (%)	Yield (ee) (*S*)-alcohol **1** (%)	Yield (ee) (*R*)-ester **2a** (%)
Amano PS	49	n.d. (28)	n.d. (31)
Candida rugosa	37	n.d. (17)	n.d. (16)
Candida antarctica	49	23 (86)	45 (96)



Scheme 4.

Table 2
Acetylation of (*R*/*S*)-**1** in the presence of *C. antarctica* lipase in different solvents

Compounds **1**	*n*	Solvent	Conversion (%)	Yield[a] (ee) (*R*)-alcohols **1** (%)	Yield[a] (ee) (*S*)-esters **2** (%)
1a	6	Pentane	53	n.d. (77)[b]	n.d. (88)[c]
1a	6	Cyclohexane	52	n.d. (79)[b]	n.d. (87)[c]
1a	6	TBME	49	54 (86)[b]	68 (96)[c]
1b	12	TBME	53	96 (76)[d]	89 (92)[d]
1c	14	TBME	52	84 (72)[d]	82 (96)[d]

[a] Calculated on the basis of theoretical yield of 50%.
[b] Determined by chiral GC after acetylation.
[c] Determined by chiral GC.
[d] Determined by ^{19}F NMR spectroscopy after transformation to Mosher esters.

2.2. Determination of the enantiomeric excesses and absolute configuration

The enantiomeric excess of the ester **2a** was determined gas chromatographically (GC) using a β-cyclodextrin capillary. The enantiomers of the ester were base-line separated. The difference in retention time was about 1 min. The enantiomeric alcohols **1a** were not separated on several different chiral GC phases, and thus were quantitatively acetylated (acetic anhydride, pyridine) prior to the GC determination of the enantiomeric excess.

The *C. antarctica* lipase-catalyzed kinetic resolution of racemic compound **1a** was most efficient in *tert*-butylmethyl ether (TBME). However, on scale up of the reaction, the enantiomeric excess of the ester and the alcohol dropped down. With 2 mmol batch, 94% ee was observed for the ester, while a 10 mmol batch delivered the ester with only 79% ee. According to these results, the alcohols with longer chains **1b** and **1c** were resolved in several small scale batches under the same conditions and TBME was used as a solvent (Table 2).

The absolute configuration of the ester obtained by *C. antarctica* lipase-catalyzed acetylation in TBME (entry 3 in Table 2) of the alcohol **1a** was determined by circular dicroism (CD) spectroscopy [30] using (−)-3-acetoxy-2-fluorodec-1-ene (−)-(**2a**) in acetonitrile (see Fig. 1) and proved by ^{1}H and ^{19}F NMR spectroscopy using Mosher esters (see discussion below).

As shown in Fig. 1, the CD-spectrum of (−)-**2a** is positive from 210 to 245 nm (n → π* of the carbonyl group; the π → π* transition, $\lambda_{max} \sim 200$ nm, has not been used for this qualitative determination of the absolute configuration), suggesting the (*S*)-configuration [31]. This agrees with the average curve of the calculated CD spectra of the five most stable conformers **A**–**E** of the model compound (*S*)-3-acetoxy-2-fluorobut-1-ene (Fig. 2).

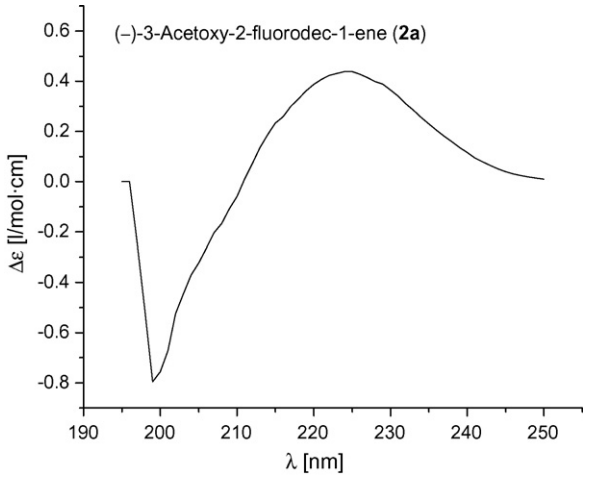


Fig. 1. CD-spectrum of (−)-**2a** (1.0 M in acetonitrile).

Compound **2a** is a conformationally flexible molecule, a property which has to be considered carefully when assignment of absolute configurations based on comparisons of theoretical and experimental chiroptical data are made (for recent examples of non-fluorinated small-to-medium organic molecules see ref. [32]). For a model system of **2a** with a methyl instead of the heptyl group, we first performed a detailed conformational search at a force-field level as described in detail recently [33]. The five energetically lowest-lying conformers were then subsequently optimized at the DFT level using a large Gaussian TZVP AO basis [34] and the non-empirical PBE density functional [35]. Inclusion of the heptyl group would produce artifacts due to the existence of many energetically low-lying, chiral (folded) conformations that are expected to be averaged out under the experimental conditions. All computations were carried out with the TURBOMOLE program system [36].

The CD spectra for the individual conformers were then computed at the TDDFT level [37–39] employing the PBE0

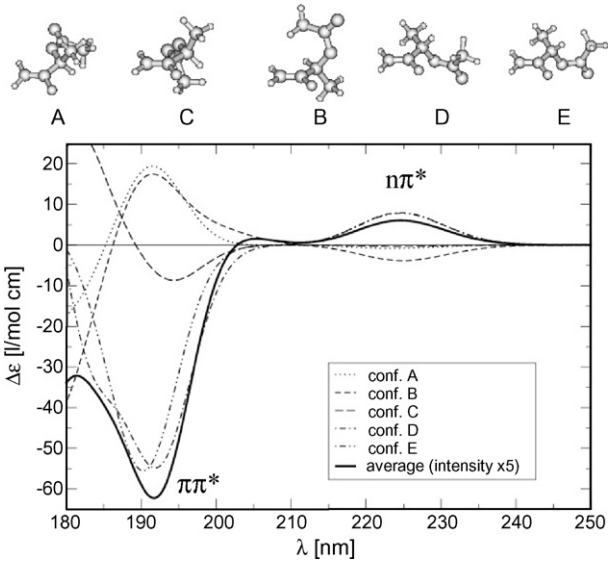


Fig. 2. Calculated CD spectra of the model compound's conformers.

functional [40] and the aug-cc-pVDZ AO basis set [41]. The conformational (relative) energies at this level were also used to compute the Boltzmann populations of conformers at room temperature and subsequently to weight the individual computed CD spectra. In all calculations, it was necessary to account for solvation effects by the COSMO continuum model [42] with a dielectric constant of 36.2 (acetonitrile). Because the molecular dipole moments change considerably between the conformers (by about 2–3 Debye) and the experiments have been conducted in acetonitrile. Inclusion of solvation effects is mandatory for this system because changes of relative energies of 0.5–1 kcal/mol compared to the gas phase have been observed.

The optimized structures of the conformers **A**–**E** are shown in Fig. 2. The relative energies of **B** and **C** are identical within our numerical accuracy while **A**, **D** and **E** are higher in energy by 0.82, 0.34 and 0.42 kcal/mol, respectively. The Boltzmann populations at 298 K are 7.6%, 30.3%, 30.3%, 17.1% and 14.7% for **A**–**E**. Fig. 2 shows the computed CD spectra for the individual conformers and with a bold line the average at room temperature. In these simulations, individual electronic transitions have been broadened by Gaussian curves with a full width at 1/*e* height of 0.4 eV and are red-shifted by 0.25 eV that accounts for methodological errors of the TDDFT-PBE0/aug-cc-pVDZ treatment.

As can be clearly seen in Fig. 2, the experimentally observed two Cotton effects at about 225 nm (nπ*) and 200 nm (ππ*) with positive and negative signs are reproduced by our computations which leads to the assignment of the absolute configuration of (−)-**2a** as (*S*). Note, that the CD of the dominating conformers **B** and **C** cancels to a large extend and that the overall signal is more determined by **D** and **E**. At this point, we want to mention that this compound is a borderline case for the assignment of absolute configuration by comparison of theoretical and experimental CD spectra. The main problem is the inherent error for the conformational energies of such polar molecules in solution which may be on the order of 0.2–0.3 kcal/mol. When the CD spectra of the individual conformers are very different, this leads to large uncertainties in the averaged spectra.

In order to prove the assignment of enantiomers, the modified Mosher's method [43] was also employed for the determination of the absolute configuration of (−)-**1a** obtained by *C. antarctica* lipase-catalyzed resolution of (*R*/*S*)-**2a** (Table 1) using the (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester. As shown in Fig. 3, positive Δδ's are located on the right-hand side and negative Δδ's are on the left-hand side of the MTPA plain. The absolute value of the Δδ is inversely proportional to the distance between the protons and the MTPA group. Therefore, the (*S*)-configuration of C-3 of (−)-**1a** has been confirmed.

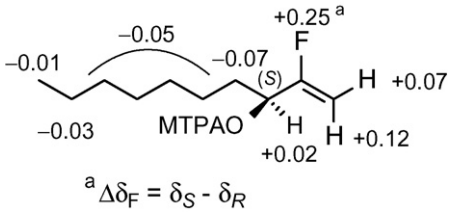


Fig. 3. Determination of the absolute configuration of (−)-**1a** by the modified Mosher's method [43] ($\Delta\delta_H = \delta_S - \delta_R$).

Analogously also the longer-chain compounds (*S*)-(−)-**2b** and (*S*)-(−)-**2c** were obtained by *C. antarctica* lipase-catalyzed acetylation of the corresponding alcohols **1b** and **1c** (see Table 2). Neither the alcohols nor the esters could be separated by chiral GC. Hence, the enantiomeric excesses were determined by ^{19}F NMR spectroscopy after transformation to the corresponding Mosher esters. The CD spectra of the esters (*S*)-(−)-**2b** and (*S*)-(−)-**2c** are very similar in shape to that of (*S*)-(−)-**2a**. Thus, as expected, the absolute configuration of these compounds is also (*S*).

Consequently, the *C. antarctica* lipase-catalyzed acetylation of **1a–c** gave the (*S*)-(−)-esters **2a–c**. Considering the priority of substituents in the CIP-system these results are in accordance with the Kazlauskas rule [44,45] for the enantiopreference of many serine proteases like the lipases employed in the present study.

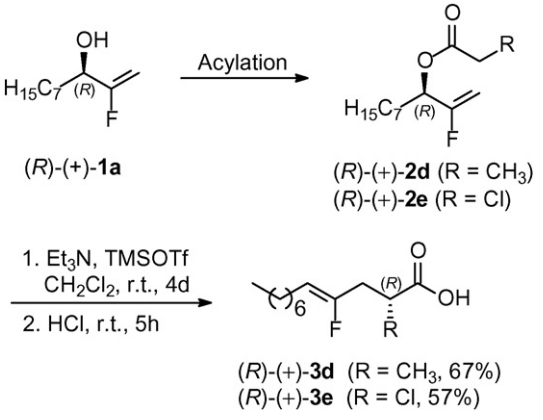
2.3. Esterification of 2-fluoroalk-1-en-3-ols

The enantioenriched alcohol (*R*)-(−)-**1a** prepared from racemic **1a** by *C. antarctica* lipase (see Table 2) was esterified either with chloroacetyl anhydride/pyridine/catalytic dimethylaminopyridine (DMAP) or with propanoic acid/dicyclohexyl carbodiimide (DCC)/catalytic DMAP (Scheme 5) [46,47].

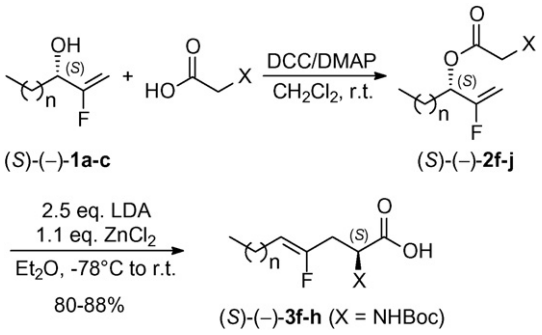
Similarly from the allylic alcohols (*S*)-(−)-**1a–c**, prepared from the acetates (*S*)-(−)-**2a–c** by $LiAlH_4$ reduction (alkaline hydrolysis led to partial racemization), by treatment with Boc-glycine or with trifluoropropanoic acid, respectively, in the presence of DCC/DMAP the corresponding Boc-glycinates (*S*)-(−)-**2f–h** or the (*S*)-(−)-2-fluoroalk-1-en-3-yl-(3,3,3)-trifluoropropionates (*S*)-(−)-**2i,j** were prepared in good yields (Scheme 6; Table 3).

2.4. Claisen-type rearrangements

The enantioenriched esters (*R*)-(+)-**2d** and (*R*)-(+)-**2e** were rearranged under the optimized conditions found for fluorinated



Scheme 5.



Scheme 6.

Table 3
Esterification of allylic alcohols (*S*)-(−)-**1a–c** to esters (*S*)-(−)-**2f–j**

Entry	Alcohol (*S*)-(−)-**1**	*n*	X	Ester (*S*)-(−)-**2**	Yield (%) (% ee)
1	**1a**	6	NHBoc	**2f**	95 (93)
2	**1b**	12	NHBoc	**2g**	93 (92)
3	**1c**	14	NHBoc	**2h**	91 (96)
4	**1b**	12	CF_3	**2i**	76 (92)
5	**1c**	14	CF_3	**2j**	75 (96)

allylic esters [9] giving the optically active α-substituted carboxylic acids (*R*)-(+)-**3d** and (*R*)-(+)-**3e** in moderate yields (Scheme 5).

The enantiomeric excess of the 2-methyl derivative (*R*)-(+)-**3d** was determined by chiral GC (β-cyclodextrin) after transformation to the methyl ester using diazomethane, while the ee of the 2-chloro compound (*R*)-(+)-**3e** could not be determined, because the methyl ester was not stable in chiral GC. Also ^1H and ^{13}C NMR shift experiments with chiral Lewis acids such as $Eu(hfc)_3$ led to line broadening, but no signal separation of the formed diastereomeric complexes was observed. Moreover, the esterification of the 2-chlorocarboxylic acid with (−)-menthol and subsequent ^1H and ^{19}F NMR investigations of the crude product did not allow doubtless integration of any signal of the diastereomers. However, the isolated 2-chloro-4-fluorodec-4-enecarboxylic acid is optically active as shown by its optical rotation of +1.9 ($CHCl_3$). Thus, chirality transfer occurred, but it could not be proved whether a partial racemization happened.

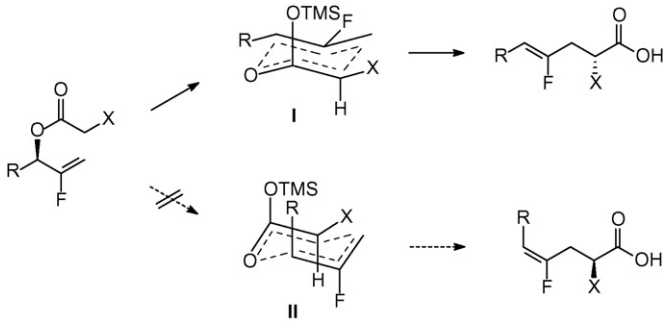


Fig. 4. Mechanism of the Ireland-Claisen rearrangement of (*R*)-2-fluoroalk-1-en-3-yl esters.

Table 4
Results of the rearrangements of glycine esters (*S*)-(−)-**2f–h**

R	Esters	ee (ester) (%)	Products	Yield (%)	ee (products)[a] (%)
C_7H_{15}	**2f**	93	**3f**	88	92
$C_{13}H_{27}$	**2g**	92	**3g**	80	92
$C_{15}H_{31}$	**2h**	96	**3h**	86	94

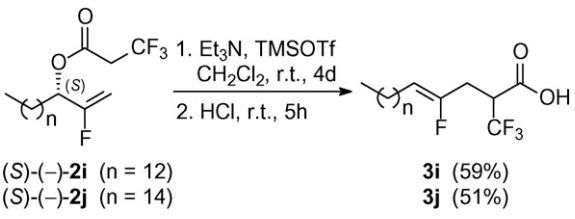
[a] The enantiomeric excess of the Boc-protected amino acids **3** was determined ^{19}F NMR spectroscopically after derivatization with optically pure (−)-menthol [49].

The mechanism of these rearrangements is shown in Fig. 4. In the first step, a *cis*-configured ester enolate is formed [9]. In this transition state **I** most of the substituents are attached in equatorial position. This six-membered transition state leads to a (*Z*)-configured double bond and (*R*)-configuration of the α-carbon. The absolute configuration was not formally established but follows from the similar rearrangements of non-fluorinated compounds [14]. The transition state **II** is less favored because of steric repulsion of the OTMS and the long alkyl chain R. Thus, the (*R*)-carboxylic acids **3** with (*Z*)-double bond are formed highly stereoselective.

This result shows that the chirality transfer from C-3 of the allylic ester to the C-2 of the carboxylic acid is possible also without stabilization of the intermediary *cis*-configured ester enolate by chelation, which was postulated by Kazmaier for the chirality transfer experiments he did with non-fluorinated amino acid allylic esters [48].

Similarly, we also rearranged *N*-protected glycine esters of different chain lengths derived from fluorinated allylic alcohols (*S*)-(−)-**2f–h** (Scheme 6). In these reactions, the corresponding *N*-protected fluorinated amino acids (*S*)-(−)-**3f–h** were obtained in high yield and without any loss in the enantiomeric purity. The results of these transformations are summarized in Table 4. Rearrangements of the corresponding (*R*)-enantiomers gave similar results [49]. In contrast, corresponding *N*-methylglycine esters failed to be rearranged under similar conditions [49].

The rearrangement of the trifluoropropionic esters (*S*)-(−)-**2i,j** under the same conditions gave the corresponding 2-trifluoromethylcarboxylic acids **3i,j** in moderate yields, however, as racemic compounds (Scheme 7). Obviously, the α-hydrogen in these products is very acidic leading to racemization under the weakly basic reaction conditions. Indeed, the α-hydrogen of the model compound 2-trifluoromethylpropionic acid was calculated to be almost 10 magnitudes more acidic than 2-methylpropionic acid.



Scheme 7.

3. Conclusion

Lipase-catalyzed resolution was shown to be useful for the preparation of optically active 2-fluoroalk-1-en-3-ols **1**. The lipase from *C. antarctica* was the most efficient out of three microbial lipases in terms of enantioselectivity. Lipase-catalyzed transesterification of the fluorinated allylic alcohols **1** with vinyl acetate in organic medium was superior over the hydrolysis in a phosphate buffer of corresponding acetates **2**. The former acetylation gave (*S*)-(−)-3-acetoxy-2-fluoroalk-1-enes, (*S*)-(−)-**2a–c**, of chain lengths C_{10}, C_{16} and C_{18} with 68–89% yield and 92–96% ee, while the remaining (*R*)-(+)-2-fluoroalk-1-en-3-ols, (*R*)-(+)-**1a–c**, were isolated with 54–96% yield and 72–86% ee. Thus, the enantiopreference for the fluorinated allylic alcohols was that predicted by the Kazlauskas rule for the selectivity of serine proteases. The absolute configuration of the (−)-allylic acetates **2a–c** was assigned to be (*S*) by CD spectroscopy and comparison with the average CD spectrum calculated for the five most stable conformers of (*S*)-3-acetoxy-2-fluorobut-1-ene as a model compound. For (−)-**2a** the absolute configuration was established unambiguously by ^{1}H and ^{19}F NMR spectroscopy using a modified Mosher's method. The optically active fluorinated allylic alcohols **1** were transferred to corresponding propionates, 3,3,3-trifluoropropionates and Boc-glycinates using the DCC/DMAP variant of esterification. Applying optimized conditions for fluorinated vinyl esters of Ireland-Claisen-type rearrangements [11], complete chirality transfer was observed from C-3 of the allylic ester **2d** to C-2 of the carboxylic acid **3d** or from allylic esters **2f–h** to 2-amino acids **3f–h**, respectively. In contrast, racemic 2-(trifluoromethyl)alk-4-enecarboxylic acids **3i,j** were formed from the optically active allylic trifluoropropionates (*S*)-(−)-**2i,j**. This result is due to the different acidities of the α-protons in the products. The weakly basic conditions of the propionate and trifluoropropionate rearrangements with triethylamine/trimethylsilyltriflate (TMSOTf) led to enolization and hence racemization in case of the formed 4-fluoro-2-(trifluoromethyl)alk-4-encarboxylic acids **3i,j**, while the corresponding 2-methyl derivative **3d** is configurationally stable under these conditions. The Boc-glycinates **2f–h** were rearranged in the presence of LDA as a base and $ZnCl_2$ as chelating metal salt. These conditions did not cause racemization and the formed 2-Boc-amino-4-fluoroalk-4-enecarboxylic acids **3f–h** were isolated without loss of optical purity.

4. Experimental

4.1. General

NMR spectra were recorded at 300 or 500 MHz (^{1}H), at 75 MHz (^{13}C) and 282 or 254 MHz (^{19}F) and are reported in ppm downfield from TMS (^{1}H and ^{13}C, $CDCl_3$ as internal standard, $\delta = 77.0$ ppm), or $CFCl_3$ (^{19}F). Mass spectra were recorded by GC/MS coupling (EI, 70 eV). ESI spectra were recorded using a Micromass Quattro LC-Z apparatus. Gas chromatographic analyses were performed using a column HP-5 (30 m, Ø 0.32 mm, film 0.25 μm, carrier gas N_2) or SPB-1 (30 m, Ø 0.32 mm, film 0.25 μm, carrier gas N_2). Thin-layer chromatography (TLC) was performed on coated silica gel plates Merck 60. The spots were detected with alkaline $KMnO_4$ solution or cerium(IV) ammonium nitrate solution. Column chromatography (silica gel, Merck 60, 0.063–0.2 mm) was used for purification of products. All reactions involving air-sensitive agents were conducted under argon atmosphere applying the Schlenk technique. All reagents purchased from suppliers were used without further purification. CH_2Cl_2 was dried and distilled over P_2O_5, Et_2O was dried and distilled over sodium, and toluene was dried by azeotropic distillation, followed by distillation over sodium. Solvents for chromatography were distilled prior to use. The fluorinated allylalcohols **1a–c** were prepared as described recently [9]. The Boc-protected amino acids are commercially available.

4.2. Synthesis of (S)-(−)-2-fluorodec-1-en-3-ol, (S)-(−)-*1a* and (R)-(+)-3-acetoxy-2-fluorodec-1-ene, (R)-(+)-*2a*

4.2.1. Lipase-catalyzed hydrolyses of (R/S)-3-acetoxy-2-fluorodec-1-ene (*2a*)

3-Acetoxy-2-fluorodec-1-ene (**2a**) [9] (460 mg, 2 mmol) was suspended in a phosphate buffer (60 mL, pH 7) and treated with the corresponding lipases *P. cepacia* (Amano PS), *C. rugosa* and *C. antarctica* (Novozym435®) (20 mg), respectively. The reactions were quenched after approximately 50% conversion by separation of the lipase. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was dried ($MgSO_4$) and the solvent was evaporated. The ratio of ester **2a** and alcohol **1a** in the crude mixture was determined gas chromatographically (Table 1). Subsequently the products were separated by column chromatography and the enantiomeric excess (ee) of the ester **2a** was determined by chiral gas chromatography (Table 1). Analogously, the ee of the alcohol **1a** was determined after acetylation with acetic anhydride in pyridine in the presence of catalytic amount of DMAP. The chemical yield was determined only for the Novozym435® catalyzed resolution after 49% conversion of **2a** (19 h). Yield: 45.2 mg (23%), (*S*)-(−)-**1a** (86% ee); 204.7 mg (0.89 mmol, 45%), (*R*)-(+)-**2a** (96% ee). The spectroscopic data agree with those for the racemic compounds [9,20].

4.2.2. Candida antarctica lipase-catalyzed hydrolysis of (R/S)-3-acetoxy-2-fluorodec-1-ene (*2a*) and subsequent Mitsunobu reaction

Analogously to the precedent procedure, racemic 3-acetoxy-2-fluorodec-1-ene (**2a**) [9] (920 mg, 4 mmol) in the phosphate buffer (pH 7, 120 mL) was resolved with *C. antarctica* lipase (40 mg). The reaction was quenched at approximately 50% conversion after 19 h. The mixture was extracted with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and the solvent was evaporated. The crude product was dissolved in diethyl ether (3 mL) and treated with triphenylphosphine (0.62 g, 2.4 mmol) and acetic acid (0.15 g, 2.4 mmol). Diethylazodicarboxylate (0.375 mL, 2.4 mmol) was added dropwise under vigorous stirring at 0 °C, while a

voluminous precipitate of triphenylphosphine oxide was formed. After slow warming to rt and stirring at this temperature for 1 h, silica gel (1 g) was added and the solvent was evaporated. The solid residue was purified by column chromatography (column 1.5 × 8 cm, cyclohexane/ethyl acetate, 40:1). Yield: 212 mg (29%) of (*R*)-(+)-**2a**, 74% ee (GC). The spectroscopic data agree with those of the racemic compound [9].

*4.3. Synthesis of (R)-(+)-2-fluoroalk-1-en-3-ols, (R)-(+)-**1**, and (S)-(−)-3-acetoxy-2-fluoroalk-1-enes, (S)-(−)-**2***

*4.3.1. Lipase-catalyzed esterification of 2-fluoroallylic alcohols **1** (general procedure)*

The corresponding racemic 2-fluoroallylic alcohol **1** (1 mmol) was dissolved in *tert*-butyl methylether (5 mL), treated with vinyl acetate (172 mg, 2.0 mmol) and *C. antarctica* lipase (Novozym 435®, 146 mg) was added. The suspension was stirred at rt and the conversion was followed by gas chromatography. The reaction was stopped at approximately 50% conversion by filtration of the immobilized lipase. The solvent was evaporated and the products were isolated as described below for the specific reaction.

*4.3.1.1. Resolution of 2-fluorodec-1-en-3-ol (**1a**).* According to the general procedure from 2-fluorodec-1-en-3-ol (**1a**) [20] (174 mg, 1.0 mmol) and vinyl acetate (172 mg, 2.0 mmol) after 48% conversion (20 h) and column chromatography of the product mixture (column 1 × 10 cm, cyclohexane/ethyl acetate, 80:1) (*S*)-(−)-3-acetoxy-2-fluorodec-1-ene, (*S*)-(−)-**2a** and (*R*)-(+)-2-fluorodec-1-en-3-ol, (*R*)-(+)-**1a** were isolated. Yields: 70 mg (68%) (*S*)-(−)-**2a**, $[\alpha]_D^{20} = -30.3$ (c = 1.29, $CHCl_3$), 96% ee (GC) and 50 mg (54%) (*R*)-(+)-**1a**, $[\alpha]_D^{20} = +6.2$ (c = 1.03, $CHCl_3$), 83% ee (GC). The spectroscopic data agree with those of the racemic compounds [9,20].

Upscaling to 10 mmol led to drop of the enantiomeric excess of the ester (*S*)-(−)-**2a** (79% ee). Thus, six parallel transformations were done in 1 mmol scale. The crude product mixtures were combined and separated by column chromatography (column 3 × 25 cm, cyclohexane/ethyl acetate, 9:1) to give the ester and the alcohol as colorless liquids. Yield: 364 mg (56%) of (*S*)-(−)-**2a**, $[\alpha]_D^{20} = -27.85$ (c = 0.99, $CHCl_3$, 93% ee) and 390 mg (75%) of (*R*)-(+)-**1**, $[\alpha]_D^{20} = +5.11$ (c = 1.04, $CHCl_3$, 80% ee).

*4.3.1.2. Resolution of 2-fluorohexadec-1-en-3-ol (**1b**)*

According to the general procedure in 16 parallel reactions 2-fluorohexadec-1-en-3-ol (**1b**) [9] (each 258 mg, 1 mmol) was acetylated with vinyl acetate in the presence of *C. antarctica* lipase and the combined product mixture was treated as described above. The products were separated by column chromatography (column 4 × 25 cm, cyclohexane/ethyl acetate, gradient 20:1 to 5:1) and isolated as colorless liquid or white solid, respectively. The enantiomeric excess was determined using Mosher's acid (see below).

*4.3.1.2.1. (S)-(−)-3-Acetoxy-2-fluorohexadec-1-ene, (S)-(−)-**2b**.* Yield: 2.13 g (89%), $[\alpha]_D^{20} = -19.58$ (c = 1.01, $CHCl_3$, 92% ee). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 16-CH_3), 1.21–1.38 (m, 22 H, 5-CH_2 to 15-CH_2), 1.67–1.77 (m, 2 H, 4-CH_2), 2.08 (s, 3 H, 18-CH_3), 4.53 (dd, $^2J_{H,H}$ = 3.1 Hz, $^3J_{H,F}$ = 48.3 Hz, 1 H, *trans*-1-CH_2), 4.71 (dd, $^2J_{H,H}$ = 3.2 Hz, $^3J_{H,F}$ = 16.7 Hz, 1 H, *cis*-1-CH_2), 5.27 (dt, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,F}$ = 16.3 Hz, 1 H, 3-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-16), 21.0 (q, C-18), 22.7 (t, C-15), 25.0 (t, C-5), 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 31.1, 31.9 (t, C-4, C-6 to C-14), 71.5 (dd, $^2J_{C,F}$ = 30.3 Hz, C-3), 92.5 (dt, $^2J_{C,F}$ = 17.7 Hz, C-1), 162.8 (d, $^1J_{C,F}$ = 262.1 Hz, C-2), 169.9 (s, C-17). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.7 (ddd, $^3J_{F,H}$ = 16.1 Hz, $^3J_{F,H}$ = 16.8 Hz, $^3J_{F,H}$ = 48.4 Hz, 1 F, F-2). GC/MS (70 eV): *m/z* (%) 300 (0) [M^+], 271 (1) [$M^+-C_2H_5$], 258 (59) [$M^+-C_2H_2O$], 257 (2) [$M^+-C_3H_7$], 240 (10) [$M^+-C_2H_4O_2$], 220 (3) [240-HF], 211 (61) [$C_{14}H_{27}O^+$], 194 (3) [$C_{14}H_{26}^+$], 187 (3) [$M^+-C_8H_{17}$], 180 (10) [$C_{13}H_{24}^+$], 173 (5) [$M^+-C_9H_{19}$], 166 (3) [$C_{12}H_{22}^+$], 159 (5) [$M^+-C_{10}H_{21}$], 152 (3) [$C_{11}H_{20}^+$], 137 (5) [$C_{10}H_{17}^+$], 135 (7), 132 (15), 131 (20) [$M^+-C_{12}H_{25}$], 118 (13) [$C_5H_7FO_2^+$], 113 (18), 109 (25) [$C_8H_{13}^+$], 107 (16) [$C_8H_{11}^+$], 97 (44) [$C_7H_{13}^+$], 95 (36), 86 (45) [$C_5H_7F^+$], 83 (53) [$C_6H_{11}^+$], 81 (41), 69 (57) [$C_5H_9^+$], 67 (64) [$C_5H_7^+$], 57 (83) [$C_4H_9^+$], 55 (91) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (81) [$C_3H_5^+$].

*4.3.1.2.2. (R)-(+)-2-Fluorohexadec-1-en-3-ol, (R)-**1b**.* Yield: 1.99 g (96%). mp 36 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = +3.22$ (c = 1.16, $CHCl_3$, 76% ee). The spectroscopic data agree with those of the racemic compound [9].

*4.3.1.3. Resolution of 2-fluorooctadec-1-en-3-ol (**1c**)*

According to the general procedure in 10 parallel reactions of 2-fluorooctadec-1-en-3-ol (**1c**) (each 286 mg, 1 mmol) were acetylated with vinyl acetate in the presence of *C. antarctica* lipase and the combined product mixture was treated as described above. The products were separated by column chromatography (column 4 × 25 cm, cyclohexane/ethyl acetate, gradient 20:1 to 5:1) and isolated as white solids. The enantiomeric excess was determined using Mosher acid (see below).

*4.3.1.3.1. (S)-(−)-3-Acetoxy-2-fluorooctadec-1-ene, (S)-(−)-**2c**.* Yield: 1.34 g (82%). mp 26 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = -19.23$ (c = 1.03, $CHCl_3$, 96% ee). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H}$ = 6.6 Hz, 3 H, 18-CH_3), 1.20–1.37 (m, 26 H, 5-CH_2 to 17-CH_2), 1.67–1.78 (m, 2 H, 4-CH_2), 2.08 (s, 3 H, 20-CH_3), 4.53 (dd, $^2J_{H,H}$ = 3.1 Hz, $^3J_{H,F}$ = 48.5 Hz, 1 H, *trans*-1-CH_2), 4.71 (dd, $^2J_{H,H}$ = 3.2 Hz, $^3J_{H,F}$ = 16.7 Hz, 1 H, *cis*-1-CH_2), 5.27 (dt, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,F}$ = 16.3 Hz, 1 H, 3-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-18), 21.0 (q, C-20), 22.7 (t, C-17), 25.0 (t, C-5), 29.2, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 31.1, 31.9 (t, C-4, C-6 to C-16), 71.5 (dd, $^2J_{C,F}$ = 31.2 Hz, C-3), 92.6 (dt, $^2J_{C,F}$ = 18.0 Hz, C-1), 162.8 (d, $^1J_{C,F}$ = 261.1 Hz, C-2), 169.9 (s, C-17). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.7 (ddd, $^3J_{F,H}$ = 16.3 Hz, $^3J_{F,H}$ = 16.7 Hz, $^3J_{F,H}$ = 48.6 Hz, 1 F, F-2). GC/MS (70 eV): *m/z* (%) 328 (0) [M^+], 299 (1) [$M^+-C_2H_5$], 286 (40) [$M^+-C_2H_2O$], 285 (3) [$M^+-C_3H_7$], 268 (9) [$M^+-C_2H_4O_2$], 248 (3) [268-HF], 239 (41) [$C_{16}H_{31}O^+$], 222 (4) [$C_{16}H_{30}^+$], 208 (9) [$C_{15}H_{28}^+$], 194 (3) [$C_{14}H_{26}^+$], 187 (3) [$M^+-C_{10}H_{21}$], 180 (4) [$C_{13}H_{24}^+$], 173 (5)

[$M^+-C_{11}H_{23}$], 166 (4) [$C_{12}H_{22}^+$], 159 (3) [$M^+-C_{12}H_{25}$], 152 (3) [$C_{11}H_{20}^+$], 137 (6) [$C_{10}H_{17}^+$], 135 (7), 132 (13), 131 (14) [$M^+-C_{14}H_{29}$], 118 (7) [$C_5H_7FO_2^+$], 113 (12), 109 (23) [$C_8H_{13}^+$], 107 (11) [$C_8H_{11}^+$], 97 (31) [$C_7H_{13}^+$], 95 (36), 86 (40) [$C_5H_7F^+$], 83 (36) [$C_6H_{11}^+$], 81 (40), 69 (45) [$C_5H_9^+$], 67 (60) [$C_5H_7^+$], 57 (68) [$C_4H_9^+$], 55 (79) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (94) [$C_3H_5^+$].

*4.3.1.3.2. (R)-(+)-2-Fluorooctadec-1-en-3-ol, (R)-(+)-**1c***. Yield: 1.21 g (84%). mp 43 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = +1.20$ ($c = 1.06$, $CHCl_3$, 72% ee). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, $^3J_{H,H} = 6.9$ Hz, 3 H, 18-CH_3), 1.19–1.43 (m, 26 H, 5-CH_2 to 17-CH_2), 1.57-1.74 (m, 2 H, 4-CH_2), 1.80 (br s, 1 H, OH), 4.12 (ddd, $^3J_{H,H} = 5.5$ Hz, $^3J_{H,H} = 7.3$ Hz, $^3J_{H,F} = 12.8$ Hz, 1 H, 3-CH), 4.53 (ddd, $^4J_{H,H} = 0.6$ Hz, $^2J_{H,H} = 3.0$ Hz, $^3J_{H,F} = 49.6$ Hz, 1 H, *trans*-1-CH_2), 4.65 (dd, $^2J_{H,H} = 3.1$ Hz, $^3J_{H,F} = 17.4$ Hz, 1 H, *cis*-1-CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q, C-18), 22.7 (t, C-17), 25.2 (t, C-5), 29.4, 29.4, 29.5, 29.6, 29.6, 29.7 (t, C-6 to C-15), 31.9 (t, C-4), 34.1 (t, C-16), 70.4 (dd, $^2J_{C,F} = 31.7$ Hz, C-3), 90.0 (dt, $^2J_{C,F} = 17.4$ Hz, C-1), 166.8 (d, $^1J_{C,F} = 261.2$ Hz, C-2). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.8 (ddd, $^3J_{F,H} = 12.6$ Hz, $^3J_{F,H} = 17.5$ Hz, $^3J_{F,H} = 49.7$ Hz, 1 F, F-2). GC/MS (70 eV): *m/z* (%) 286 (0) [M^+], 268 (6) [M^+-HF], 250 (2) [$C_{18}H_{34}^+$], 248 (2) [$C_{18}H_{32}^+$], 239 (10), 222 (4) [$C_{16}H_{30}^+$], 221 (3), 208 (6) [$C_{15}H_{28}^+$], 194 (4) [$C_{14}H_{26}^+$], 180 (4) [$C_{13}H_{24}^+$], 166 (6) [$C_{12}H_{22}^+$], 152 (7) [$C_{11}H_{20}^+$], 137 (8) [$C_{10}H_{17}^+$], 135 (10), 123 (12) [$C_9H_{15}^+$], 109 (22) [$C_8H_{13}^+$], 103 (8) [$M^+-C_{13}H_{27}^+$], 97 (32) [$C_7H_{13}^+$], 95 (33), 86 (31) [$C_5H_7F^+$], 83 (40) [$C_6H_{11}^+$], 81 (41), 75 (33) [$M^+-C_{15}H_{31}$], 67 (69) [$C_5H_7^+$], 57 (80) [$C_4H_9^+$], 55 (83) [$C_4H_7^+$], 43 (99) [$C_3H_7^+$], 41 (100) [C_3H_5].

4.3.2. Reduction of (S)-(−)-3-acetoxy-2-fluoroalk-1-enes **2** with $LiAlH_4$

In a dried round bottom flask $LiAlH_4$ (84 mg, 2.2 mmol, 2.2 eq) was suspended in dry diethyl ether (15 mL) and the corresponding fluorovinyl acetate **2** (1 mmol) in dry diethyl ether (10 mL) was added slowly under stirring at 0 °C. Then the mixture was refluxed for 4 h and cooled to 0 °C. Water (15 mL) was added very carefully, the colloidal precipitate was dissolved with aq. HCl and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 10 mL) and the combined organic layer was washed with brine (15 mL). After drying ($MgSO_4$) the solvent was evaporated and the product was purified as given for the specific case.

*4.3.2.1. (S)-(−)-2-Fluorodec-1-en-3-ol, (S)-(−)-**1a***. According to the general procedure, (*S*)-(−)-3-acetoxy-2-fluorohexadec-1-ene, (*S*)-(−)-**2a**, (1.37 g, 6.35 mmol) was reduced. After column chromatography (column 4 × 7 cm, cyclohexane/ethyl acetate, 20:1) (*S*)-(−)-**1a** was isolated as a colorless liquid. Yield: 923 mg (84%). $[\alpha]_D^{20} = -4.56$ ($c = 1.11$, $CHCl_3$, 93% ee). The spectroscopic data agree with those of the racemic compound [20].

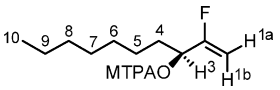
*4.3.2.2. (S)-(−)-2-Fluorohexadec-1-en-3-ol, (S)-(−)-**1b***. According to the general procedure, (*S*)-(−)-3-acetoxy-2-fluorohexadec-1-ene, (*S*)-(−)-**2b**, (1.50 g, 5 mmol) was reduced. After column chromatography (column 4 × 18 cm, cyclohexane/ethyl acetate, 10:1) (*S*)-(−)-**1b** was isolated as a white waxy solid. Yield: 1.10 g (86%). mp 37 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = -2.38$ ($c = 1.01$, $CHCl_3$, 92% ee). The spectroscopic data agree with those of the racemic compound [9].

*4.3.2.3. (S)-(−)-2-Fluorooctadec-1-en-3-ol, (S)-(−)-**1c***. According to the general procedure, (*S*)-3-acetoxy-2-fluorooctadec-1-ene, (*S*)-(−)-**2c**, (1.12 g, 3.41 mmol) was reduced. After column chromatography (column 3 × 20 cm, cyclohexane/ethyl acetate, 10:1) (*S*)-(−)-**1c** was isolated as a white solid. Yield: 926 mg (95%). mp 47 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = -2.84$ ($c = 1.05$, $CHCl_3$, 96% ee). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H} = 6.7$ Hz, 3 H, 18-CH_3), 1.19–1.43 (m, 26 H, 5-CH_2 to 17-CH_2), 1.55–1.73 (m, 2 H, 4-CH_2), 1.76 (br s, 1 H, OH), 4.12 (ddd, $^3J_{H,H} = 5.6$ Hz, $^3J_{H,H} = 7.0$ Hz, $^3J_{H,F} = 13.0$ Hz, 1 H, 3-CH), 4.52 (dd, $^2J_{H,H} = 3.1$ Hz, $^3J_{H,F} = 49.6$ Hz, 1 H, *trans*-1-CH_2), 4.64 (dd, $^2J_{H,H} = 3.0$ Hz, $^3J_{H,F} = 17.5$ Hz, 1 H, *cis*-1-CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-18), 22.7 (t, C-17), 25.2 (t, C-5), 29.4, 29.5, 29.6, 29.7 (t, C-6 to C-15), 31.9 (t, C-4), 34.0 (t, C-16), 70.4 (dd, $^2J_{C,F} = 30.1$ Hz, C-3), 90.0 (dt, $^2J_{C,F} = 17.7$ Hz, C-1), 166.9 (d, $^1J_{C,F} = 260.6$ Hz, C-2). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −111.8 (ddd, $^3J_{F,H} = 13.0$ Hz, $^3J_{F,H} = 17.4$ Hz, $^3J_{F,H} = 49.8$ Hz, 1 F, F-2). GC/MS (70 eV): *m/z* (%) 286 (0) [M^+], 268 (6) [M^+-HF], 250 (2) [$C_{18}H_{34}^+$], 248 (3) [$C_{18}H_{32}^+$], 239 (9), 222 (4) [$C_{16}H_{30}^+$], 221 (4), 208 (6) [$C_{15}H_{28}^+$], 194 (4) [$C_{14}H_{26}^+$], 180 (4) [$C_{13}H_{24}^+$], 166 (6) [$C_{12}H_{22}^+$], 152 (7) [$C_{11}H_{20}^+$], 137 (10) [$C_{10}H_{17}^+$], 135 (10), 123 (13) [$C_9H_{15}^+$], 109 (21) [$C_8H_{13}^+$], 103 (16) [$M^+-C_{13}H_{27}^+$], 97 (26) [$C_7H_{13}^+$], 95 (27), 86 (31) [$C_5H_7F^+$], 83 (40) [$C_6H_{11}^+$], 81 (41), 75 (40) [$M^+-C_{15}H_{31}$], 67 (66) [$C_5H_7^+$], 57 (87) [$C_4H_9^+$], 55 (71) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (82) [C_3H_5].

4.3.3. Determination of the enantiomeric excesses via Mosher esters (general procedure)

The corresponding enantiomers of alcohols **1** (0.1 mmol) and dicyclohexyl carbodiimide (DCC, 35 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (2 mL) and treated with (*S*)-(−)-α-methoxy-α-trifluormethylphenylacetic acid (39 mg, 0.16 mmol) dissolved in CH_2Cl_2 (2 mL). Shortly after a white precipitate started to appear. A catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) was added and the suspension was stirred at rt overnight. Then the suspension was mixed with pentane (20 mL), filtered and the solid was washed with pentane (20 mL). The combined organic layer was washed with water (3 × 10 mL), 5% acetic acid (3 × 10 mL) and water again (3 × 10 mL). After drying ($MgSO_4$) and evaporation of the solvent the crude product was investigated by ^{19}F NMR spectroscopy. The ratio of the diastereomers was determined by integration of the signals in the ^{19}F NMR spectra (see Tables 1 and 2). The identity of the Mosher esters was proved by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry after column chromatography (column 2 × 15 cm, cyclohexane/ethyl acetate 40:1) [49].

Table 5
^{1}H and ^{19}F NMR data of the MTPA esters of (−)-**1a** (δ, $CDCl_3$)



Atom no.	(*S*)-MTPA	(*R*)-MTPA	Δδ (ppm)[a]
1a	4.812	4.744	+0.07
1b	4.649	4.530	+0.12
3	5.485	5.470	+0.02
4	1.753	1.821	−0.07
5–8	1.214	1.260	−0.05
9	1.274	1.305	−0.03
10	0.874	0.880	−0.01
F	−111.785	−111.538	+0.25

[a] ($\Delta\delta_H = \delta_S - \delta_R$); ($\Delta\delta_F = \delta_S - \delta_R$).

*4.3.3.1. Determination of the absolute configuration of (−)-**1a***

According to the procedure given in paragraph 4.3.3. the diastereomeric Mosher esters of compound (−)-**1a** were prepared. The ^{1}H and ^{19}F NMR data of these compounds are given in Table 5. As an example, additional data of the (*S*,*S*)-diastereomer are given below.

4.3.3.1.1. (S)-2-Fluorodec-1-en-3-yl (S)-2-methoxy-2-trifluoromethyl-2-phenylacetate. Prepared according to the general procedure from (*S*)-(−)-2-fluorodec-1-en-3-ol (16.9 mg, 97.1 μmol) and (*S*)-MTPA chloride (27.3 mg, 106 μmol) as a colorless oil. Yield: 22.6 mg (60%). $[\alpha]_D^{27} = -57.7$ ($c = 0.700$, $CHCl_3$). ^{13}C NMR: δ 14.4 (CH_3), 22.9 (CH_2), 24.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 30.9 (CH_2), 31.9 (CH_2), 55.7 (OCH_3), 73.7 (d, $^{2}J_{CF} = 31$ Hz, O-*C*H-CF), 77.4 (H_3CO-*C*-CF_3), 94.4 (d, $^{2}J_{CF} = 17$ Hz, H_2C=*C*F), 123.4 (q, $^{1}J_{CF} = 288$ Hz, CF_3) 127.3 (Ar-CH), 128.5 (3 Ar-CH), 129.7 (Ar-CH), 132.2 (Ar-C), 161.4 (d, $^{1}J_{CF} = 261$ Hz, H_2C=*C*F), 165.9 (C = O). MS: *m/z* 391 (M^++1), 390 (M^+). Exact mass: calcd. for $C_{20}H_{26}F_4O_3$ (M^+): 390.1819; found 390.1817.

4.4. Synthesis of 2-fluoroallylic esters **2**

4.4.1. (R)-(+)-2-fluoro-3-propionoxydec-1-ene, (R)-(+)-**2d**

According to the general procedure [9], (*R*)-(+)-2-fluordec-1-en-3-ol, (*R*)-(+)-**1a**, (350 mg, 2.0 mmol) was esterified with propanoic acid and DCC/DMA. Yield: 412 mg (90%). The spectroscopic data agree with those of the racemic compound [9].

4.4.2. (R)-(+)-3-Chloroacetoxy-2-fluorodec-1-ene, (R)-(+)-**2e**

According to the general procedure [9], (*R*)-(+)-2-fluorodec-1-en-3-ol, (*R*)-(+)-**1a** (522 mg, 3.0 mmol, 83% ee) was esterified with chloroacetic anhydride in pyridine/DMAP. Yield: 806 mg (91%). The spectroscopic data agree with those of the racemic compound [9].

4.4.3. Synthesis of Boc-glycine esters **2f–h**

*4.4.3.1. (S)-(−)-2-Fluorodec-1-en-3-yl-N-Boc-glycinate, (S)-(−)-**2f**.* According to the general procedure [11], (*S*)-(−)-2-fluorohexadec-1-en-3-ol, (*S*)-(−)-**1a** (696 mg, 4 mmol, 93% ee) was reacted with Boc-glycine (771 mg, 4.4 mmol). The product was purified by column chromatography (3 × 15 cm, cyclohexane/ethyl acetate, 5:1) and isolated as a colorless liquid. Yield: 1.25 g (95%). $[\alpha]_D^{20} = -21.00$ ($c = 1.06$, $CHCl_3$, 93% ee). The spectroscopic data agree with those of the racemic compound [11].

*4.4.3.2. (R)-(+)-2-Fluorodec-1-en-3-yl-N-Boc-glycinate (R)-(+)-**2f**.* According to the general procedure [11], (*R*)-(+)-2-fluorohexadec-1-en-3-ol, (*R*)-(+)-**1a**, (390 mg, 2.24 mmol, 80% ee) was reacted with Boc-glycine (432 mg, 2.46 mmol). The product was purified by column chromatography (3 × 11 cm, cyclohexane/ethyl acetate, 5:1) and isolated as a colorless liquid. Yield: 625 mg (84%). $[\alpha]_D^{20} = +16.78$ ($c = 0.50$, $CHCl_3$, 80% ee). The spectroscopic data agree with those of the racemic compound [11].

*4.4.3.3. (S)-(−)-2-Fluorohexadec-1-en-3-yl-N-Boc-glycinate (S)-(−)-**2g**.* According to the general procedure [11], (*S*)-(−)-2-fluorohexadec-1-en-3-ol, (*S*)-(−)-**1b** (552 mg, 2.14 mmol, 92% ee) was reacted with Boc-glycine (412 mg, 2.35 mmol). The product was purified by column chromatography (3 × 25 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a colorless liquid. Yield: 830 mg (93%). $[\alpha]_D^{20} = -16.65$ ($c = 1.02$, $CHCl_3$, 92% ee). The spectroscopic data agree with those of the racemic compound [11].

*4.4.3.4. (R)-(+)-2-Fluorohexadec-1-en-3-yl-N-Boc-glycinate (R)-(+)-**2g**.* According to the general procedure [11], (*R*)-(+)-2-fluorohexadec-1-en-3-ol, (*R*)-(+)-**1b** (1.03 g, 4.0 mmol, 76% ee) was reacted with Boc-glycine (771 mg, 4.4 mmol). The product was purified by column chromatography (3 × 30 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a colorless liquid. Yield: 1.40 g (84%). $[\alpha]_D^{20} = +14.93$ ($c = 1.03$, $CHCl_3$, 76% ee). The spectroscopic data agree with those of the racemic compound [11].

*4.4.3.5. (S)-(−)-2-Fluorooctadec-1-en-3-yl-N-Boc-glycinate (S)-(−)-**2h**.* According to the general procedure [11], (*S*)-(−)-2-fluorooctadec-1-en-3-ol, (*S*)-(−)-**1c** (740 mg, 2.59 mmol, 96% ee) was reacted with Boc-glycine (497 mg, 2.85 mmol). The product was purified by column chromatography (4 × 30 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a white solid. Yield: 1.04 g (91%). mp 25–26 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = -15.72$ ($c = 1.03$, $CHCl_3$, 96% ee).

*4.4.3.6. (R)-(+)-2-Fluorooctadec-1-en-3-yl-N-Boc-glycinate (R)-(+)-**2h**.* According to the general procedure [11], (*R*)-(+)-2-fluorooctadec-1-en-3-ol, (*R*)-(+)-**1c** (1.11 g, 3.89 mmol, 72% ee) was reacted with Boc-glycine (750 mg, 4.28 mmol). The product was purified by column chromatography (3 × 30 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a colorless liquid. Yield: 1.62 g (94%). $[\alpha]_D^{20} = +10.59$ ($c = 1.01$, $CHCl_3$, 72% ee).

*4.4.3.7. (S)-(−)-2-Fluorohexadec-1-en-3-yl-(3,3,3-trifluoropropionate) (S)-(−)-**2i**.* According to the general procedure

[11], (*S*)-(−)-2-fluorohexadec-1-en-3-ol, (*S*)-(−)-**1b** (516 mg, 2 mmol, 92% ee) was reacted with 3,3,3-trifluoropropanoic acid (307 mg, 2.4 mmol, 1.2 eq). The product was purified by column chromatography (4 × 20 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a colorless oil. Yield: 559 mg (76%). $[\alpha]_D^{20} = -18.60$ ($c = 0.84$, $CHCl_3$, 92% ee). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H} = 6.6$ Hz, 3 H, 16-CH_3), 1.20–1.39 (m, 22 H, 5-CH_2 to 15-CH_2), 1.77 (m, 2 H, 4-CH_2), 3.20 (q, $^3J_{H,F} = 10.0$ Hz, 2 H, 18-CH_2), 4.58 (dd, $^2J_{H,H} = 3.3$ Hz, $^3J_{H,F} = 48.1$ Hz, 1 H, *trans*-1-CH_2), 4.76 (dd, $^2J_{H,H} = 3.3$ Hz, $^3J_{H,F} = 16.5$ Hz, 1 H, *cis*-1-CH_2), 5.32 (dt, $^3J_{H,H} = 7.0$ Hz, $^3J_{H,F} = 16.3$ Hz, 1 H, 3-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-16), 22.7 (t, C-15), 24.8 (t, C-5), 29.1, 29.4, 29.5, 29.6, 29.7, 30.9 (t, C-4, C-6 to C-13), 31.9 (t, C-14), 39.8 (qt, $^2J_{C,F} = 31.3$ Hz, C-18), 73.0 (dd, $^2J_{C,F} = 33.0$ Hz, C-3), 93.4 (dt, $^2J_{C,F} = 17.8$ Hz, C-1), 123.3 (q, $^1J_{C,F} = 276.9$ Hz, C-19), 161.8 (d, $^1J_{C,F} = 260.8$ Hz, C-2), 163.1 (q, $^3J_{C,F} = 4.1$ Hz, C-17). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −112.1 (ddd, $^3J_{F,H} = 16.4$ Hz, $^3J_{F,H} = 16.6$ Hz, $^3J_{F,H} = 48.1$ Hz, 1 F, F-2), −64.0 (t, $^3J_{F,H} = 10.0$ Hz, 3 F, F-19). GC/MS (70 eV): *m/z* (%) 368 (0.1) [M^+], 348 (0.2) [M^+−HF], 258 (13) [$C_{16}H_{31}FO^+$], 240 (6) [258-H_2O], 211 (14) [$C_{14}H_{27}O^+$], 186 (10) [$C_6H_6F_4O_2^+$], 149 (7) [$C_{11}H_{17}^+$], 137 (8) [$C_{10}H_{17}^+$], 135 (11) [$C_{10}H_{15}^+$], 113 (25) [$C_8H_{17}^+$], 111 (100) [$C_3H_2F_3O^+$], 99 (24) [$C_7H_{15}^+$], 97 (37) [$C_7H_{13}^+$], 95 (38) [$C_7H_{11}^+$], 86 (84) [$C_5H_7F^+$], 83 (56) [$C_2H_2F_3^+$] 69 (68) [CF_3^+], 67 (42) [86-F], 57 (70) [$C_4H_9^+$], 55 (71) [$C_4H_7^+$], 43 (47) [$C_3H_7^+$], 41 (32) [$C_3H_5^+$].

*4.4.3.8. (S)-(−)-2-Fluorooctadec-1-en-3-yl-(3,3,3-trifluoropropionate) (S)-(−)-**2j**.* According to the general procedure [11], (*S*)-(−)-2-fluorooctadec-1-en-3-ol, (*S*)-(−)-**1c** (572 mg, 2 mmol, 96% ee) was reacted with 3,3,3-trifluoropropanoic acid (307 mg, 2.4 mmol, 1.2 eq). The product was purified by column chromatography (4 × 20 cm, cyclohexane/ethyl acetate, 10:1) and isolated as a colorless oil. Yield: 594 mg (75%). $[\alpha]_D^{20} = -14.14$ ($c = 0.92$, $CHCl_3$, 96% ee). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H} = 6.7$ Hz, 3 H, 18-CH_3), 1.19–1.39 (m, 26 H, 5-CH_2 to 17-CH_2), 1.77 (m, 2 H, 4-CH_2), 3.20 (q, $^3J_{H,F} = 10.0$ Hz, 2 H, 20-CH_2), 4.58 (dd, $^2J_{H,H} = 3.3$ Hz, $^3J_{H,F} = 48.1$ Hz, 1 H, *trans*-1-CH_2), 4.75 (dd, $^2J_{H,H} = 3.3$ Hz, $^3J_{H,F} = 16.5$ Hz, 1 H, *cis*-1-CH_2), 5.34 (dt, $^3J_{H,H} = 6.9$ Hz, $^3J_{H,F} = 16.3$ Hz, 1 H, 3-CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-18), 22.7 (t, C-17), 24.8 (t, C-5), 29.1, 29.4, 29.5, 29.6, 29.7, 30.9 (t, C-4, C-6 to C-15), 32.0 (t, C-16), 39.8 (tq, $^2J_{C,F} = 31.1$ Hz, C-20), 73.0 (dd, $^2J_{C,F} = 31.6$ Hz, C-3), 93.4 (dt, $^2J_{C,F} = 17.3$ Hz, C-1), 123.1 (q, $^1J_{C,F} = 277.0$ Hz, C-21), 161.8 (d, $^1J_{C,F} = 261.5$ Hz, C-2), 163.1 (q, $^2J_{C,F} = 4.4$ Hz, C-19). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −112.2 (ddd, $^3J_{F,H} = 16.1$ Hz, $^3J_{F,H} = 16.4$ Hz, $^3J_{F,H} = 47.6$ Hz, 1 F, F-2), −63.9 (t, $^3J_{F,H} = 10.0$ Hz, 3 F, F-21). GC/MS (70 eV): *m/z* (%): 396 (0.3) [M^+], 376 (1) [M^+−HF], 286 (21) [$C_{18}H_{35}FO^+$], 268 (11) [286-H_2O], 239 (19) [$C_{16}H_{31}O^+$], 199 (6) [$C_7H_7F_4O_2^+$], 186 (14) [$C_6H_6F_4O_2^+$], 149 (8) [$C_{11}H_{17}^+$], 137 (11) [$C_{10}H_{17}^+$], 135 (15) [$C_{10}H_{15}^+$], 113 (25) [$C_8H_{17}^+$], 111 (100) [$C_3H_2F_3O^+$], 99 (26) [$C_7H_{15}^+$], 97 (44) [$C_7H_{13}^+$], 95 (41) [$C_7H_{11}^+$], 86 (87) [$C_5H_7F^+$], 83 (56) [$C_2H_2F_3^+$] 69 (64) [CF_3^+], 67 (41) [86-F], 57 (75) [$C_4H_9^+$], 55 (71) [$C_4H_7^+$], 43 (58) [$C_3H_7^+$], 41 (34) [$C_3H_5^+$].

4.5. General procedure for the Ireland-Claisen rearrangements

In a dried Schlenk vessel the respective allylic ester (1.0 mmol) in dry CH_2Cl_2 (2 mL) was treated under argon with trimethylsilyltriflate (TMSOTf) (230 mg, 1.2 mmol) and triethylamine (306 mg, 3.0 mmol) and stirred at room temperature for four days, while the solution turned from colorless to dark red-brown. Then 2N HCl (7 mL) was added and the mixture was stirred vigorously for 4 h. The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). Further work-up was different for the respective products and will be mentioned below.

*4.5.1. (R)-(+)-2-Methyl-4-fluorododec-4(Z)-enoic acid, (R)-(+)-**3d***

According to the general procedure [9], (*R*)-(+)-3-propionoxy-2-acetoxy-2-fluorodec-1-ene, (*R*)-(+)-**2d** (290 mg, 1.3 mmol, 83% ee) was rearranged with TMSOTf (300 mg, 1.56 mmol) and triethylamine (398 mg, 3.9 mmol). Yield: 194 mg (67%).$[\alpha]_D^{20} = +4.5$ ($c = 1.03$, $CHCl_3$, 82% ee). The spectroscopic data agree with those for the racemic compound [9].

*4.5.2. (R)-2-Chloro-4-fluorododec-4(Z)-enoic acid (R)-(+)-**3e***

According to general procedure [9], (*R*)-(+)-3-chloroacetoxy-2-fluorodec-1-ene (*R*)-(+)-**2e** (166 mg, 0.66 mmol, 83% ee) was rearranged and the product (*R*)-(+)-**3e** was isolated as a yellowish, light sensitive oil as described earlier for the racemic compound [9]. Yield: 85 mg (51%). $[\alpha]_D^{20} = +1.9$ ($c = 0.98$, $CHCl_3$). The spectroscopic data agree with those published for the racemic one [9]. The enantiomeric excess could not be determined.

*4.5.3. (S)-(+)-N-Boc-2-amino-4-fluorododec-4(Z)-enoic acid, (S)-(+)-**3f***

According to the general procedure [11], (*S*)-(−)-2-fluorodec-1-en-3-yl-*N*-Boc-glycinate, (*S*)-(−)-**2f** (993 mg, 3 mmol, 93% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 869 mg (88%). mp 45 °C (diethyl ether). $[\alpha]_D^{20} = +19.27$ ($c = 1.08$, $CHCl_3$, 92% ee).

*4.5.4. (R)-(−)-N-Boc-2-amino-4-fluorododec-4(Z)-enoic acid, (R)-(−)-**3f***

According to the general procedure [11], (*R*)-(+)-2-fluorodec-1-en-3-yl-*N*-Boc-glycinate, (*R*)-(+)-**2f** (538 mg, 1.63 mmol, 80% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 382 mg (71%). mp 48 °C (diethyl ether). $[\alpha]_D^{20} = -16.64$ ($c = 0.92$, $CHCl_3$, 76% ee). The spectroscopic data agree with those of the racemic compound [11]. The enantiomeric excess was determined ^{19}F NMR spectroscopically via the (−)-menthylester of the crude product.

*4.5.5. (S)-(+)-N-Boc-2-amino-4-fluorooctadec-4(Z)-enoic acid, (S)-(+)-**3g***

According to the general procedure [11], (*S*)-(−)-2-fluorohexadec-1-en-3-yl-*N*-Boc-glycinate, (*S*)-(−)-**2g** (750 mg, 1.67 mmol, 92% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 554 mg (80%). mp 55 °C (pentane). $[\alpha]_D^{20} = +14.03$ (c = 1.02, $CHCl_3$, 92% ee).

*4.5.6. (R)-(−)-N-Boc-2-amino-4-fluorooctadec-4(Z)-enoic acid, (R)-(−)-**3g***

According to the general procedure [11], (*R*)-(+)-2-fluorohexadec-1-en-3-yl-*N*-Boc-glycinate, (*R*)-(+)-**2g** (1.25 g, 3 mmol, 76% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 544 mg (45%). mp 67 °C (pentane). $[\alpha]_D^{20} = -12.43$ (c = 1.02, $CHCl_3$, 76% ee). The spectroscopic data agree with those of the racemic compound [11]. The enantiomeric excess was determined ^{19}F NMR spectroscopically via the (−)-menthyl-ester of the crude product.

*4.5.7. (S)-(+)-N-Boc-2-amino-4-fluoroicos-4(Z)-enoic acid, (S)-(+)-**3h***

According to the general procedure [11], (*S*)-(−)-2-fluorooctadec-1-en-3-yl-*N*-Boc-glycinate, (*S*)-(−)-**2h** (923 mg, 2.08 mmol, 96% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 791 mg (86%). mp 61 °C (pentane). $[\alpha]_D^{20} = +13.86$ (c = 1.02, $CHCl_3$, 94% ee). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26 (m, 26 H, 7-CH_2 to 19-CH_2), 1.45 (s, 9 H, 23-CH_3), 2.05 (m, 2 H, 6-CH_2), 2.54-2.83 (m, 2 H, 3-CH_2), 4.35 (m, 0.3 H, 2-CH), 4.46 (m, 0.7 H, 2-CH), 4.63 (dt, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,F}$ = 37.2 Hz, 1 H, 5-CH), 5.17 (br d, $^3J_{H,H}$ = 7.8 Hz, 0.7 H, NH), 6.35 (br s, 0.3 H, NH), 9.78 (br s, 1 H, COOH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-20), 22.7 (t, C-19), 23.6 (dt, $^3J_{C,F}$ = 3.8 Hz, C-6), 28.3 (q, C-23), 29.2, 29.3, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7 (t, C-7 to C-17), 31.9 (t, C-18), 34.7 (dt, $^2J_{C,F}$ = 29.4 Hz, C-3), 51.2 (d, C-2), 80.3 (s, C-22), 109.9 (dd, $^2J_{C,F}$ = 15.7 Hz, C-5), 154.3 (d, $^1J_{C,F}$ = 251.8 Hz, C-4), 155.3 (s, C-21), 176.2 (s, C-1). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −112.3 (br ddd, $^3J_{F,H}$ = 17.9 Hz, $^3J_{F,H}$ = 20.3 Hz, $^3J_{F,H}$ = 38.3 Hz, 0.3 F, F-4), −111.1 (ddd, $^3J_{F,H}$ = 18.7 Hz, $^3J_{F,H}$ = 20.1 Hz, $^3J_{F,H}$ = 38.6 Hz, 0.7 F, F-4). ESI-MS (+) in CH_3OH: *m/z* (%): 466 (100) [M^++Na]. Analysis calcd. for $C_{25}H_{46}FNO_4$ (443.6) C, 67.68; H, 10.45; N, 3.16. Found: C, 67.87; H, 10.59; N, 3.00.

*4.5.8. (R)-(−)-N-Boc-2-amino-4-fluoroicos-4(Z)-enoic acid, (R)-(−)-**3h***

According to the general procedure [11], (*R*)-(+)-2-fluorooctadec-1-en-3-yl-*N*-Boc-glycinate, (*R*)-(+)-**2h** (1.57 g, 3.53 mmol, 72% ee) was rearranged. The product was isolated as a white solid after recrystallization. Yield: 658 mg (42%). mp 71 °C (pentane). $[\alpha]_D^{20} = -12.29$ (c = 1.08, $CHCl_3$, 73% ee).

*4.5.9. 4-Fluoro-2-(trifluoromethyl)octadec-4(Z)-enoic acid (**3i**)*

According to the general procedure [9], (*S*)-(−)-2-fluorohexadec-1-en-3-yl-(3,3,3-trifluoro-propionate), (*S*)-(−)-**2i**, (272 mg, 0.74 mmol, 92% ee) in dry CH_2Cl_2 (3 mL) under argon was treated with TMSOTf, (266 mg, 1.2 mmol) and triethylamine (306 mg, 3 mmol). The solution was refluxed 24 h. After usual work-up the product was isolated as a white solid after recrystallization. Yield: 162 mg (59%). mp 45 °C (pentane). $[\alpha]_D^{20} = 0$ (c = 1.13, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.19-1.39 (m, 22 H, 7-CH_2 to 17-CH_2), 2.05 (m, 2 H, 6-CH_2), 2.63–2.88 (m, 2 H, 3-CH_2), 3.45 (m, 1 H, 2-CH), 4.69 (dt, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,F}$ = 37.1 Hz, 1 H, 5-CH), 9.97 (br s, 1 H, COOH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-18), 22.7 (t, C-17), 23.6 (dt, $^3J_{C,F}$ = 2.8 Hz, C-6), 27.2 (dt, $^2J_{C,F}$ = 32.5 Hz, C-3), 29.1, 29.1, 29.2, 29.4, 29.6, 29.7 (t, C-7 to C-15), 31.9 (t, C-16), 47.9 (dq, $^2J_{C,F}$ = 28.7 Hz, C-2), 109.5 (dd, $^2J_{C,F}$ = 14.9 Hz, C-5), 124.0 (q, $^1J_{C,F}$ = 281.4 Hz, C-19), 153.4 (d, $^1J_{C,F}$ = 252.5 Hz, C-4), 171.8 (q, $^3J_{C,F}$ = 3.0 Hz, C-1). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −114.1 (ddd, $^3J_{F,H}$ = 15.2 Hz, $^3J_{F,H}$ = 20.4 Hz, $^3J_{F,H}$ = 37.4 Hz, 1 F, F-4), −68.8 (d, $^3J_{F,H}$ = 7.9 Hz, 3 F, F-19). ESI-MS (−) in CH_3OH: *m/z* (%) 367 [M^+−H]. Exact mass: calcd. for $C_{19}H_{31}F_4O_2$: 367.2266; found 367.2279.

*4.5.10. 4-Fluoro-2-(trifluoromethyl)icos-4(Z)-enoic acid (**3j**)*

According to the general procedure [9], (*S*)-(−)-2-fluorooctadec-1-en-3-yl-(3,3,3-trifluoropropionate), (*S*)-(−)-**2j** (396 mg, 1 mmol, 96% ee) was rearranged and isolated as a white solid after recrystallization. Yield: 202 mg (51%), mp 37 °C (pentane), $[\alpha]_D^{20} = 0$ (c = 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.19–1.45 (m, 26 H, 7-CH_2 to 19-CH_2), 2.05 (m, 2 H, 6-CH_2), 2.68 (ddd, $^3J_{H,H}$ = 5.2 Hz, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,F}$ = 15.0 Hz, 1 H, 3-CH_2), 2.78 (ddd, $^3J_{H,H}$ = 9.6 Hz, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,F}$ = 21.0 Hz, 1 H, 3-CH_2), 3.43 (m, 1 H, 2-CH), 4.69 (dt, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,F}$ = 37.2 Hz, 1 H, 5-CH), 10.27 (br s, 1 H, COOH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q, C-20), 22.7 (t, C-19), 23.6 (dt, $^3J_{C,F}$ = 4.1 Hz, C-6), 27.2 (dt, $^2J_{C,F}$ = 32.1 Hz, C-3), 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7 (t, C-7 to C-17), 32.0 (t, C-18), 48.0 (dq, $^2J_{C,F}$ = 28.2 Hz, C-2), 109.5 (dd, $^2J_{C,F}$ = 16.7 Hz, C-5), 123.9 (q, $^1J_{C,F}$ = 280.6 Hz, C-21), 153.4 (d, $^1J_{C,F}$ = 251.3 Hz, C-4), 172.0 (q, $^3J_{C,F}$ = 2.6 Hz, C-1). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −114.1 (ddd, $^3J_{F,H}$ = 15.0 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 37.3 Hz, 1 F, F-4), −68.8 (d, $^3J_{F,H}$ = 8.7 Hz, 3 F, F-21). ESI-MS (−) in CH_3OH: *m/z* (%) 395 (100) [M^+−H]. Exact mass: calcd. for $C_{21}H_{35}F_4O_2$ 395.2579; found 395.2570.

4.6. Determination of the enantiomeric excess of the Boc-amino acids

The corresponding crude Boc-amino acid **3** (0.1 mmol) and DCC (72 mg, 0.3 mmol) were dissolved in dry CH_2Cl_2 (2 mL) and treated with (−)-menthol (45 mg, 0.3 mmol). Subsequently, a catalytic amount of DMAP was added and the mixture was stirred at rt overnight. Then pentane (5 mL) was added under stirring and the white precipitate was filtered off. The solvent was evaporated and the ratio of the crude diastereomers was investigated by ^{19}F NMR spectroscopy (see Table 4).

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