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Synthesis of (9*R*)- and (9*S*)-10-Fluorodecan-9-olide (Fluoro-Phoracantholide I) First Lipase-catalyzed Enantioselective Esterification of β-Fluoroalcohols

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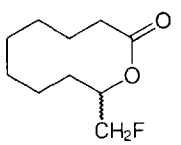
Abstract: Synthesis of both enantiomers of fluoro-phoracantholide I, namely (9*S*)-10-fluorodecan-9-olide ((9*S*)-(-)-**1**) and (9*R*)-10-fluorodecan-9-olide (9*R*)-(+)-**1**, has been achieved through lipase-catalyzed enantioselective acetylation of methyl 10-fluoro-9-hydroxydecanoate (**2a**) with acetic anhydride in the presence of Lipase Amano PS (*Pseudomonas cepacia*). The higher homologue, methyl 11-fluoro-10-hydroxyundecanoate (**2b**) has also been resolved. These enzymatic resolutions by acetylation of ω-fluoro-(ω-1)-hydroxyalkanoic acid esters of long-chain fatty acids represent the first lipase-catalyzed enantioselective esterifications of β-fluoroalcohols.

Introduction

Recently vicinal fluorohydrins and especially secondary β-fluoroalcohols have become the subject of interest in organofluorine chemistry[1] as they act as precursors in the synthesis of biologically active, monofluorinated analogues of natural compounds[2]. In 1994 we showed that ω-fluoro-(ω-1)-hydroxyalkanoic acid esters of long-chain fatty acids can easily be converted into medium to large ring monofluorinated lactones, a novel class of monofluorinated fatty acid derivatives[3]. By our methodology, including regioselective hydrofluorination of terminally oxirane-precursors and subsequent cyclisation of the resulting vicinal fluorohydroxy fatty acids, a racemic monofluorinated pheromone analogue of one of the three major components of the metasternal gland secretion of the eucalypt longicorn (*Phoracantha synonyma*)[4], namely (±)-10-fluorodecan-9-olide (**1**) [(±)-fluoro-phoracantholide I], was obtained[3].



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Any biological activity or any process of molecular recognition is strongly related to the stereochemistry of the active compound. Moreover, each enantiomer can lead to different effects when interacting with

receptors[5]. Synthesis of potentially active monofluorinated compounds should therefore always utilize methods to address both enantiomers of the compound. Over the past ten years the use of enzymes in organic synthesis for the purpose of kinetic resolution of racemates has proven to be superior to the classical methods of resolution by fractional crystallization of derived diastereomers or by chromatography using chiral stationary phases[6]. This is especially true for the utilization of enzymatic procedures in organic media employing immobilized enzymes[7]. Despite this recent rapid development, only a few examples of enzymatic hydrolysis involving monofluorinated compounds have been found[8] and, to the best of our knowlegde, only one example for an enzymatic esterification of a fluorinated alcohol, namely naphtyl trifluoromethyl carbinol, has been reported to date[9].

Results and discussion

Herein we report the enzymatic resolution of the secondary β-fluoroalcohols methyl 10-fluoro-9-hydroxydecanoate (**2a**) and methyl 11-fluoro-10-hydroxyundecanoate (**2b**) as the first examples for enzymatic esterifications of monofluorinated alcohols in organic media. Furthermore, we summarize the subsequent synthesis of both enantiomers of 10-fluorodecan-9-olide (fluoro-phoracantholide I), (9*S*)-(-)-**1** and (9*R*)-(+)-**1** in high enantiomeric excesses and chemical yields.

The racemic methyl ω-fluoro-(ω-1)-hydroxyalkanoates *rac*-**2a** and *rac*-**2b** were synthesized according to our previous work[3]. To a solution of *rac*-**2a** and *rac*-**2b**, respectively, and one equivalent of acetic anhydride in toluene the lipase of *Pseudomonas cepacia* (Lipase Amano PS, LAPS), immobilized[10] on Celite® 577, was added. The reaction mixture was magnetically stirred at room temperature and followed by GLC analysis. After 20 to 26 hours nearly 50% conversion was reached. The alcohols could easily be separated from the acetates by chromatography. All products have a positive specific rotation (figure 1).

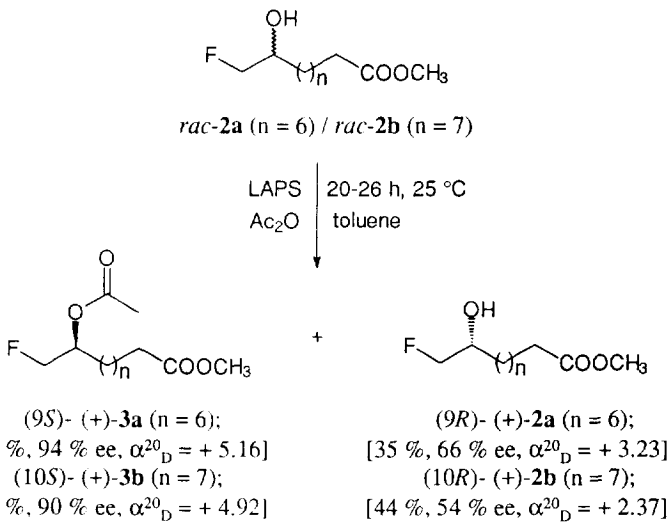


Figure 1: Enzymatic acetylation of *rac*-**2a** und *rac*-**2b** with LAPS/Ac_2O in toluene

The determination of the enantiomeric excess (ee) by GLC analysis on different cyclodextrin-phases[11] was unsuccessful so far, as no base-line separation of the signals of the enantiomers could be realized. To determine the ee´s of our products we therefore developed a new method employing $^{1}H,^{19}F$-decoupled ^{19}F-NMR spectroscopy using europium(III)-tris(heptafluoropropylcamphorate) ($Eu(hfc)_3$) as a shift reagent. The resonances of the heptafluoropropyl groups (-75 to -150 ppm) do not disturb the signals of the monofluorinated compounds **2a** and **2b** found in the area of < -200 ppm. Hence, in this special ^{19}F-NMR-experiment using 0.5 equivalents of $Eu(hfc)_3$, the $^{1}H,^{19}F$-decoupled ^{19}F-NMR spectra of **2a** and **2b**, respectively, were measured solely in the area from -150 to -250 ppm, a tripled resolution of signals and clean base-line separation of the peaks of the diastereomeric complexes was seen. By this method all ee´s could be readily determined by integration of the separated resonances. 0.5 equivalents of the shift reagent leads to a splitting of about 50 Hz and even 0.25 eq. of $Eu(hfc)_3$ results in a separation of about 30 Hz. As figure 1 points out, the acetates **3a** (94% ee) and **3b** (90% ee) are obtained in high chemical yields and enantiomeric excesses; the remaining alcohols **2a** (66% ee) and **2b** (54% ee) are obtained in good chemical yields and moderate enantiomeric excesses. Thus, enzymatic esterification of a β-monofluorinated secondary alcohol is shown to be an excellent method for the kinetic resolution of ω-fluoro-(ω-1)-hydroxy fatty acid esters. The proposed absolute stereochemistry of the acetates and alcohols, namely methyl (9*S*)-(+)-10-fluoro-9-acetoxydecanoate ((9*S*)-(+)-**3a**), methyl (10*S*)-(+)-11-fluoro-10-acetoxyundecanoate ((10*S*)-(+)-**3b**), (9*R*)-(+)-10-fluoro-9-hydroxydecanoate ((9*R*)-(+)-**2a**) and (10*R*)-(+)-11-fluoro-10-hydroxyundecanoate ((10*S*)-(+)-**2b**), could not be established by X-ray crystallography because of the lack of good crystals; however the stereochemistry was confirmed by the comparison of the results of CD-spectroscopy[12] of (10*S*)-(+)-**3b** and the empirical rule of Kazlauskas et al.[13] for the enantio-preference of *Pseudomonas cepacia*-lipase and especially LAPS (figure 2).

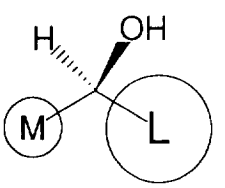


Figure 2: Modified Prelog-rule by Kazlauskas[13] for the prefered enantiomer of a secondary alcohol in lipase-catalyzed reactions (M = medium / L = large)

An UV- and subsequently a CD spectrum was measured from a $1.53 \cdot 10^{-3}$ M solution of (+)-**3b** in cyclohexane (d = 0.5 cm). λ_{max} was determined as 205 nm and the CD is positive over the complete range of wavelengths. From the carboxylate-sector rules[14] relevant for the acetate-chromophores, an (*S*)-stereochemistry for the stereogenic center of the acetate is predicted based on the following assumptions: the $(CH_2)_n$-backbone in long-chain alkanes prefers a trans-anti-orientation (zig-zag-orientation), -OAc is smaller than CH_2R, the H of C_{10} and the C=O double bond both point in the same direction and the influence of the carboxylic acid moiety (C_1) can be neglected due to its large distance from the stereogenic center. Thus, the prediction of the Kazlauskas-rule (98% probability)[13] is consistent with the CD spectroscopy.

This successful first enzymatic resolution of a monofluorinated compound (figure 1) marks also the first synthesis of optically active methyl ω-fluoro-(ω-1)-acetoxy- and methyl ω-fluoro-(ω-1)-hydroxyalkanoates. Moreover, the enzyme system can also be used for the separation of the regioisomeric methyl β-fluoro-hydroxyalkanoates (figure 3).

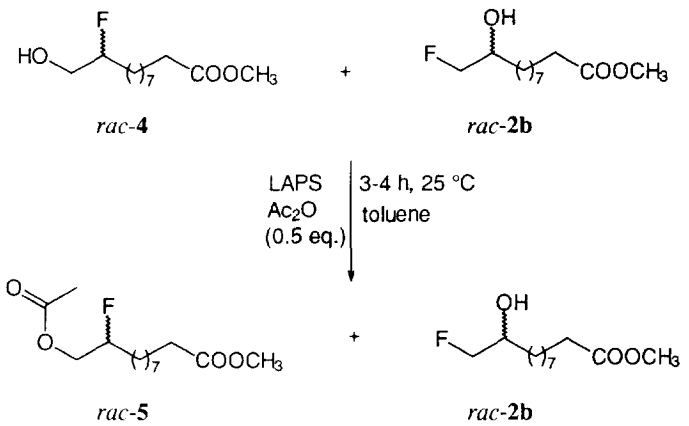


Figure 3: Regioselective enzymatic acylation of methyl 10-fluoro-11-hydroxyundecanoate (**4**) with LAPS/Ac_2O in toluene

Like the separation of racemates, a different reaction rate of the acetylated enzyme with either a primary or a secondary alcohol leads to regioselective reaction of the enzyme. In the case of the enzyme system LAPS/Ac_2O/toluene, if only 0.5 equivalent of acetic anhydride is used on a 1:1 mixture of methyl 11-fluoro-10-hydroxyundecanoate (**2b**) and its regioisomer methyl 10-fluoro-11-hydroxyundecanoate (**4**), only the primary alcohol is almost quantitatively converted into the corresponding acetate within 3 to 4 hours. The reaction proceeds too rapidly under these conditions for any additional enantiomeric differentiation, moreover the steric difference between a fluoro- and a hydrogen atom at the secondary carbon is most likely not significant for any enzymatic resolution. Therefore, we did not try to investigate this conversion under different conditions. But the regioselective course of this enzymatic reaction offers a convenient alternative for the separation of methyl ω-fluoro-(ω-1)-hydroxy- and methyl (ω-1)-fluoro-(ω)-hydroxyalkanoates compared with the original method of flash-chromatography[3].

Finally we synthesized both enantiomers of Fluoro-Phoracantholide I, namely (9*S*)-10-fluorodecan-9-olide ((9*S*)-(-)-**1**) and (9*R*)-10-fluorodecan-9-olide (9*R*)-(+)-**1**, according to the standard procedures[3] (figure 4). Both products, (9*S*)-(-)-**1** and (9*R*)-(+)-**1**, showed exactly the same enantiomeric excess (determined by ^{19}F-NMR, see above) as their precursors (9*S*)-(+)-**3a** and (9*R*)-(+)-**2a**, respectively, so no racemization occured in the final two steps of the synthesis. The synthesis of both enantiomers, and especially (9*S*)-(-)-10-Fluordecan-9-olide ((9*S*)-(-)-**1**) as the monofluorinated analogue bearing the same absolute stereochemistry as the natural (*R*)-Phoracantholide I [*Phoracantha synonyma*], offers a promising start for more sophisticated methods of biocatalysis within organofluorine chemistry.

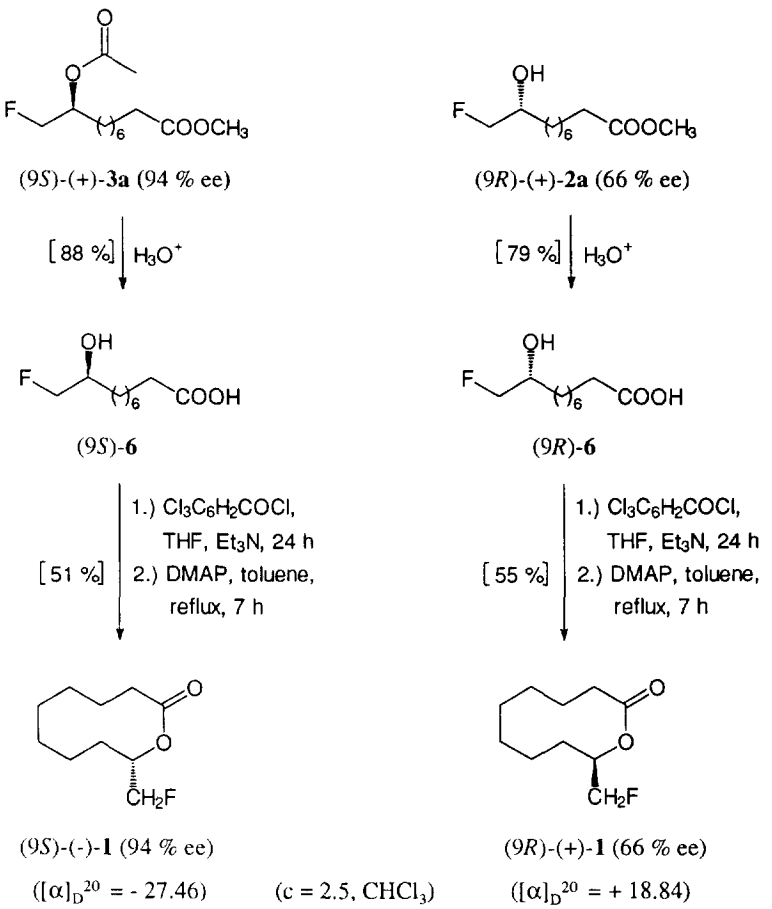


Figure 4: Synthesis[3] of both enantiomers of Fluoro-Phoracantholide I (**1**)

Experimental

Melting/boiling points: uncorrected value. - Refraction indices: C. Zeiss, Jena, Abbé refractometer. - ^{1}H (300 MHz), ^{13}C NMR (75.5 MHz): Bruker WM 300, TMS for ^{1}H and $CDCl_3$ for ^{13}C NMR as internal standard. - ^{19}F NMR: Bruker WM 300 (282.3 MHz) and Bruker AC 200 (188.0 MHz), α,α,α-trifluorotoluene (δ = -63.0 ppm from $CFCl_3$) as internal standard. - Mass spectra (70 eV): GLC/MS coupling: Varian GC 3400/Varian Saturn IT (ion trapping). - GLC: Hewlett-Packard 5890 II gas chromatograph, quartz capillary column 0.33 mm x 25 m, 0.52 µm HP-1 (Hewlett-Packard), nitrogen as carrier gas, FID detector. - Optical rotations: Perkin Elmer 241 polarimeter (Na-D-line: λ = 589 nm). - Enantiomeric excess: by ^{1}H,^{19}F-decoupled ^{19}F-NMR shift experiment [addition of 50 mol% $Eu(hfc)_3$; integration of resonance signals for the terminal fluorine substituent]. - UV- and CD spectra of **3b**: JASCO J-710 [$1.53 \cdot 10^{-3}$ M solution in cyclohexane, d = 0.5 cm]. - Elementary analyses: Mikroanalytisches Laboratorium, OC, Universität Münster. - Thin-layer chromatography: Merck silica gel DC 60 F254. - Flash chromatography: Merck silica gel 60. Methyl 10-

fluoro-9-hydroxydecanoate (**2a**), methyl 11-fluoro-10-hydroxyundecanoate (**2b**), methyl 10-fluoro-11-hydroxyundecanoate (**4**), 10-fluoro-9-hydroxydecanoic acid (**6**) and 10-fluorodecan-9-olide (**1**) have been synthesized according to known procedures[3]. Celite® 577 was obtained from Fluka and all other applied reagents were obtained from Janssen chemicals; Lipase Amano PS is a gift from Amano Pharmaceuticals. Toluene was purified by distillation.

Immobilisation of LAPS: 2 g Celite® 577 are subsequently washed with water and 0.1 N phosphate buffer. The Celite® is added with stirring to a suspension of 0.5 g Lipase Amano PS (LAPS) in 10 ml of 0.1 N phosphate buffer. This mixture is air-dried on a glass-plate and occasionally mixed up again. If neccessary, vacuum (15 Torr) can be applied. The remaining water in the light brownish power will then be approximately 1 %.

General procedure for the enzymatic resolution of methyl ω-fluoro-(ω-1)-hydroxy-alkanoates: 4.27 mmol of methyl ω-fluoro-(ω-1)-hydroxyalkanoate (±)-**2a** or (±)-**2b** and 0.4 ml (0.436 g, 4.27 mmol) of acetic anhydride are dissolved in 10 ml of distilled toluene. After the addition of 31 mg Lipase Amano PS (LAPS), absorbed on 0.126 g Celite® 577, the resulting suspension is magnetically stirred at room temperature for approximately 24 hours until 50 % conversion is reached. For reaction control 0.2 ml of the suspension is filtered over silica gel (addition of 5-10 ml toluene as eluent), neutralized with 5% $NaHCO_3$ (aq), dried and submitted to GLC analysis. After completion of the reaction the whole suspension is treated in the same manner and dried with $MgSO_4$. Chromatography on silica gel (cyclohexane/ethyl acetate = 3 : 1 as eluent) provides the methyl (*S*)-(+)-ω-fluoro-(ω-1)-acetoxyalkanoates and the (*R*)-(+)-ω-fluoro-(ω-1)-hydroxyalkanoates.

Methyl (9R)-(+)-10-fluoro-9-hydroxydecanoate ((9R)-(+)-2a): Yield: 0.329 g (1.49 mmol, 35 %). - $[\alpha]^{D}_{20}$: + 3.23 (c = 2.5, $CHCl_3$), 66 % ee (^{19}F-NMR). - All other physical and spectroscopic data have already been described[3].

Methyl (9S)-(+)-10-fluoro-9-acetoxydecanoate ((9S)-(+)-3a): 0.536 g (2.05 mmol, 48 %). - $[\alpha]^{D}_{20}$: + 5.16 (c = 2.5, $CHCl_3$), 94 % ee (^{19}F-NMR). - b.p.: 172-174 °C / 15 Torr. - n_D^{21}: 1.4733. - ^{1}H-NMR ($CDCl_3$): δ [ppm] = 1.25-1.35 (br s, 8H, aliphat. H, 4-H_2 to 7-H_2), 1.6 (br s, 4H, 3-H_2 and 8-H_2), 2.07 (s, 3H, 13-H_3), 2.29 (t, $^3J_{HH}$ = 7.6 Hz, 2H, 2-H_2), 3.65 (s 3H, 11-H_3), 4.35 (ddd, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 10.05 Hz, $^3J_{HH}$ = 6.68 Hz, 1H, 10-H_a), 4.5 (ddd, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 10.05 Hz, $^3J_{HH}$ = 5.24 Hz, 1H, 10-H_b), 5.0 (m, $^3J_{HF}$ = 21.5 Hz, 1H, 9-H). - ^{13}C-NMR ($CDCl_3$): δ [ppm] = 20.96 (q, C-13), 24.8-29.45 (6 t, C-3 to C-8), 33.97 (t, C-2), 51.36 (q, C-11), 72.25 (dd, $^2J_{CF}$ = 20.34 Hz, C-9), 83.54 (dt, $^1J_{CF}$ = 172.9 Hz, C-10), 170.5 (s, C-12), 174.12 (s, C-1). - ^{19}F-NMR ($CDCl_3$): δ [ppm] = -230.0 (dt, $^2J_{HF}$ = 47.7 Hz, $^3J_{HF}$ = 22.8 Hz, -CH(CH_2F), 10-F). - MS (GLC/MS, 70 eV, Ion Trap): m/z (%) = 243 (10) [M^+-F], 187 (15) [McLafferty], 171 (8), 155 (22) [187-CH_4O], 150 (12), 135 (10), 121 (8), 109 (35), 74 (25), 67 (25), 55 (30), 43 (100), 41 (25), 39 (18). - Elemental analysis: $C_{13}H_{23}FO_4$ (262.32): cal. C 59.52, H 8.84, found: C 59.34, H 8.84.

Methyl (10R)-(+)-11-fluoro-10-hydroxyundecanoate ((9R)-(+)-2b): Yield: 0.440 g (1.88 mmol, 44 %). - $[\alpha]^{D}_{20}$: + 2.37 (c = 2.5, $CHCl_3$), 54 % ee (^{19}F-NMR). - All other physical and spectroscopic data have already been described[3].

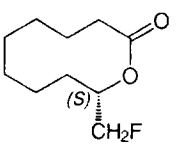
Methyl (10S)-(+)-11-fluoro-10-acetoxyundecanoate ((9S)-(+)-3b): 0.450 g (1.63 mmol, 38 %). - $[\alpha]^{D}_{20}$: + 4.92 (c = 2.5, $CHCl_3$), 90 % ee (^{19}F-NMR). - b.p.: 178-179 °C / 15 Torr. - n_D^{21}: 1.4763. - ^{1}H-NMR ($CDCl_3$): δ [ppm] = 1.3 (br s, 10H, aliphat. H, 4-H_2 to 8-H_2), 1.5-1.7 (br s, 4H, 3-H_2 and 9-H_2), 2.08

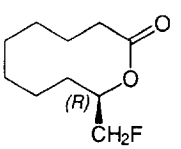
(s, 3H, 14-H_3), 2.29 (t, $^3J_{HH}$ = 7.6 Hz, 2H, 2-H_2), 3.66 (s, 3H, 12-H_3), 4.35 (ddd, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ ≅ 6.5 Hz, 1H, 11-H_a), 4.5 (ddd, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ ≅ 5 Hz, 1H, 11-H_b), 5.03 (m, $^3J_{HF}$ = 21.5 Hz, 1H, 10-H). - ^{13}C-NMR ($CDCl_3$): δ [ppm] = 20.96 (q, C-14), 24.8-25.0 (2 t, C-4 and C-9), 28.9-29.5 (5 t, C-3 and C-5 bis C-8), 34.0 (t, C-2), 51.32 (q, C-12), 72.3 (dd, $^2J_{CF}$ = 17.8 Hz, C-10), 83.55 (dt, $^1J_{CF}$ = 172.94 Hz, C-11), 170.51 (s, C-13), 174.15 (s, C-1). - ^{19}F-NMR ($CDCl_3$): δ [ppm] = -230.6 (dt, $^2J_{HF}$ = 47.7 Hz, $^3J_{HF}$ = 21.0 Hz, -CH(CH_2F), 11-F). - MS (GLC/MS, 70 eV, Ion Trap): m/z (%) = 276 (3) [M$^+$], 257 (5) [M$^+$-F], 201 (8) [McLafferty], 185 (10), 169 (8) [201-CH_4O], 164 (12), 147 (8), 135 (10), 123 (22), 107 (9), 95 (15), 81 (38), 55 (32), 43 (100). - Elemental analysis: $C_{14}H_{25}FO_4$ (276.35): cal. C 60.85, H 9.12, found: C 60.95, H 9.14.

Enzymatic, regioselective resolution of methyl ω-fluoro-(ω-1)-hydroxy- and (ω-1)-fluoro-ω-hydroxyalkanoates: 1g (4.27 mmol) of a 42 : 58 mixture of methyl 11-fluoro-10-hydroxy-undecanoate (**2b**) and methyl 10-fluoro-11-hydroxyundecanoate (**4**) is treated as described above with LAPS, but only 0.2 ml (0.22 g, 2.15 mmol) of acetic anhydride are added and the reaction is stopped after 3-4 hours. Chromatography on silica gel (cyclohexane/ethyl acetate = 3 : 1 as eluent) provides methyl (±)-10-fluoro-11-acyloxyundecanoate (**5**) and methyl (±)-11-fluoro-10-hydroxy-undecanoate (±)-**2b**.

Methyl (±)-11-fluoro-10-acetoxyundecanoate ((±)-5): 0.502 g (1.82 mmol, 43 % = 74 % of theory). - $[\alpha]^D_{20}$: 0 (c = 2.5, $CHCl_3$). - b.p.: 173-175 °C / 15 Torr. - n_D^{21}: 1.4741. - ^{1}H-NMR ($CDCl_3$): δ [ppm] = 1.3 (br s, 10H, aliphat. H, 4-H_2 to 8-H_2), 1.45-1.65 (br s, 4H, 3-H_2 and 9-H_2), 2.1 (s, 3H, 14-H_3), 2.3 (t, $^3J_{HH}$ = 7.5 Hz, 2H, 2-H_2), 3.66 (s, 3H, 12-H_3), 4.05-4.3 (2 ddd, 2H, 11-H_2), 4.65 (m, $^2J_{HF}$ = 49.6 Hz, 1H, 10-H). - ^{13}C-NMR ($CDCl_3$): δ [ppm] = 20.63 (q, C-14), 24.65-24.8 (2 t, C-4 and C-8), 29.0-29.3 (4 t, C-3 and C-5 to C-7), 31.25 (dt, $^2J_{CF}$ = 20.4 Hz, C-9), 34.0 (t, C-2), 51.3 (q, C-12), 65.75 (dt, $^2J_{CF}$ = 22.9 Hz, C-11), 91.25 (dd, $^1J_{CF}$ = 172.9 Hz, C-10), 170.61 (s, C-13), 174.1 (s, C-1). - ^{19}F-NMR ($CDCl_3$): δ [ppm] = -187.35 (m, -CHF-CH_2OAc, 10-F). - MS (GLC/MS, 70 eV, Ion Trap): m/z (%) = 257 (3) [M$^+$-F], 245 (5) [M$^+$-OCH_3], 203 (12) [245-$COCH_3$], 183 (5) [203-HF], 164 (8), 147 (5), 135 (8), 123 (15), 107 (9), 98 (18), 81 (30), 55 (22), 43 (100). - Elemental analysis: $C_{14}H_{25}FO_4$ (276.35): cal. C 60.85, H 9.12, found: C 60.76, H 9.13.

Synthesis of both enantiomers of 10-fluorodecan-9-olide (1): The free acids (9*S*)-**6** and (9*R*)-**6** were synthesized[3] and not further characterized, but directly cyclized[3] towards the lactones:





	(9*S*)-(-)-**1** [94 % ee (^{19}F-NMR)]	(9*R*)-(+)-**1** [66 % ee (^{19}F-NMR)]
Yields:	0.288 g (1.53 mmol, 51 % from (9*S*)-**6**)	0.311 g (1.65 mmol, 55 % from (9*R*)-**6**)
$[\alpha]^D_{20}$:	- 27.46 (c = 2.5, $CHCl_3$),	+ 18.84 (c = 2.5, $CHCl_3$),

All other physical and spectroscopic data are identical with the already described data of the racemate[3].

Acknowledgements

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References and Notes

1. a) J.A. Wilkinson, *Chem. Rev.* **1992**, *92*, 505-519.
   b) A. Sattler, G. Haufe, *J. Fluorine Chem.* **1994**, *69*, 185-190.
2. a) J.T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley Interscience Publications, Wiley & Sons, New York, **1991**.
   b) D.M. Huryn, M. Okabe, *Chem. Rev.* **1992**, *92*, 1745-1768.
3. A. Sattler, G. Haufe, *Liebigs Ann. Chem.* **1994**, 921-925.
4. a) B.P. Moore, W.V. Brown, *Aust. J. Chem.* **1976**, *29*, 1365-1374.
   b) T. Kitahara, K. Koseki, K. Mori, *Agric. Biol. Chem.* **1987**, *51*, 3417-3421.
5. G. Resnati, *Tetrahedron* **1993**, *49*, 9385-9445.
6. C.-S. Chen, C.J. Sih, *Angew. Chem.* **1989**, *101*, 711-724.
7. A.M. Klibanov, *Acc. Chem. Res.* **1990**, *23*, 114-120.
8. a) T. Yamazaki, M. Asai, T. Ohnogi, J.T. Lin, T. Kitazume, *J. Fluorine Chem.* **1987**, *35*, 537-553.
   b) T. Yamazaki, S. Ichikawa, T. Kitazume, *J. Chem. Soc., Chem. Commun.* **1989**, 253-255.
   c) M. Bucciarelli, A. Forni, I. Moretti, F. Prati, G. Torre, G. Resnati, P. Bravo, *Tetrahedron* **1989**, *45*, 7505-7514.
   d) K. Murata, T. Kitazume, *Tetrahedron Asymm.* **1993**, *4*, 889-892.
9. J. Gaspar, A. Guerrero, *Tetrahedron Asymm.* **1995**, *6*, 231-238.
10. D. Bianchi, P. Cesti, E. Battistel, *J. Org. Chem.* **1988**, *53*, 5531-5534.
11. Orientating experiments (carrier gas: nitrogen) were undertaken: with β-Cyclodextrin Beta-Dex™ 120 Supelco 30 m, ∅ = 0.25 mm, partial separation; Silica fused 20 m, ∅ = 0.25 mm Chiraldex B-PH, 135 °C, carrier gas He 1 ml/40 sec., partial separation; 50 m Lipodex A, 50 m Lipodex C, 20 m Chiraldex B-TA, 25 m Lipodex E, 50 m FS-Cyclodex beta I/P and 50 m FS-Cyclodex beta II/P no separation.
12. E.L. Eliel, S.H. Wilen, *Stereochemistry of Organic Compunds*, Wiley Interscience, Wiley and Sons Inc., New York **1994**.
13. a) R.J. Kazlauskas, A.N.E. Weissfloch, A.T. Rappaport, L.A. Cuccia, *J. Org. Chem.* **1991**, 56, 2656-2665.
   b) M. Cygler, P. Grochulski, R.J. Kazlauskas, J.D. Schrag, F. Bouthillier, B. Rubin, A.N. Serreqi, A.K. Gupta, *J. Am. Chem. Soc.* **1994**, 116, 3180-3186.
14. M. Legrand, M.J. Rougier in H.B. Kagan (Ed.), *Stereochemistry-Fundamentals and Methods*, Vol. 2, *Dipole Moments, CD or ORD*, G. Thieme Verlag, Stuttgart, **1977**, S. 31-183.

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