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Lipase-catalyzed resolution of 2-fluorodecanoic acid

Frank Tranel and Günter Haufe *

Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149 Münster, Germany

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Abstract

Kinetic resolutions of alkyl (±)-2-fluorodecanoates by lipase-catalyzed hydrolysis and of (±)-2-fluorodecanoic acid by lipase-catalyzed esterification are described for the first time.

1. Introduction

Optically active 2-fluoro-substituted carboxylic acids are widely used as drugs,[1] shift reagents[2] and building blocks for synthesis.[3] Several examples of the asymmetric synthesis of such compounds have been published, but mostly expensive and/or dangerous chemicals were used and frequently only one enantiomer was made accessible.[4] Especially for the application of such compounds in ferroelectric liquid crystals, fluorinated long chain carboxylic acids are of great interest.[4d,5] Lipase-catalyzed resolutions have been widely employed in this context either by hydrolysis of fluoro-substituted carboxylic esters[6] or by acetylation of 2-fluoroalcohols in non-polar solvents and subsequent oxidation of the fluorohydrins.[6a,7] In most examples the fluorine is attached to a side-chain but not at the stereogenic carbon. In some rare cases when the fluorine substituent is placed at the asymmetric center, this is a quaternary carbon. On the other hand, when fluorine is attached to a secondary carbon, the similarity of the van der Waals radii of hydrogen (1.2 Å) and fluorine (1.35 Å)[8] suggests that enzymes in general can hardly distinguish between these atoms on steric grounds. On the other hand, substitution of hydrogen by fluorine induces electronic perturbation of the molecule. Based on an Anh–Eisenstein stabilization and results of lipase-catalyzed hydrolysis of several fluoro-substituted benzhydrol acetates, O'Hagan et al. raised the question of whether it is a sterically or electronically induced discrimination.[8,9] The most impressive example for a discrimination between hydrogen and fluorine is the lipase-catalyzed kinetic resolution of ethyl 2-fluorohexanoate **1** (Scheme 1).[6g]

* Corresponding author. Fax: +49 (0)251-833 97 72; e-mail: haufe@uni-muenster.de

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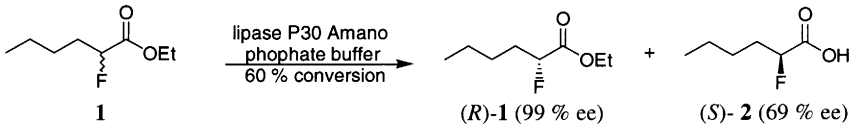


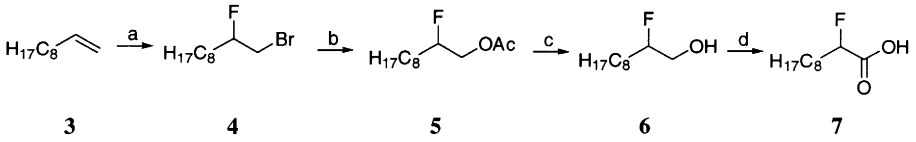
Scheme 1. Lipase-catalyzed deracemization of ethyl 2-fluorohexanoate **1**[6g]

2. Results and dicussion

We wish to report here our results on lipase-catalyzed kinetic resolution of 2-fluorocaprinic acid **7**. Compound **7** has been found to be less toxic than would have been expected for compounds which principally can undergo β-oxidation, to form highly toxic fluoroacetic acid.[10] In this case applications in medicinal chemistry might be possible.[11] Long chain α-fluorinated carboxylic acids are reported to be of special interest for the application in ferroelectric liquid crystals which have a fast growing market.[4d,5]

Racemic 2-fluorocaprinic acid **7** was first synthesized from 1-decene **3** by Pattison et al.[11] in 47% overall yield in 1965. The key-step in their synthesis was the bromofluorination of the olefin **3** in liquid HF. After bromine to acetate exchange to form **5** and saponification, the formed fluorohydrin **6** was oxidized to **7**.[7,10] Alternatively, **6** has been generated by oxirane ring opening of 1-decene oxide using Olah's reagent (70% HF in pyridine).[4b–d] The optically active acid **7** has previously been synthesized by Nohira et al. by ring opening with Olah's reagent of the expensive enantiopure 1-decene oxide in poor yield.[4b]

According to our method demonstrated for other 2-fluorocarboxylic acids,[12] racemic 2-fluorodecanoic acid **7** has been synthesized from 1-decene **3** in four steps in analytically pure form in 42% overall yield (Scheme 2) without the need of difficult to handle chemicals such as liquid HF and without any chromatography or distillation which is necessary by Nohira's method.[4b,d]



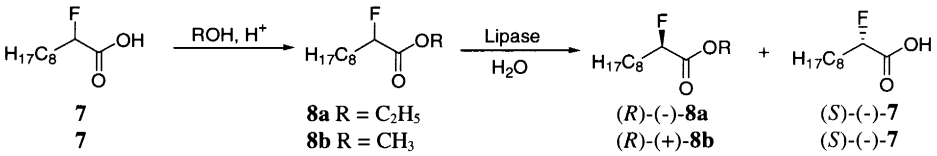
Scheme 2. Synthesis of (±)-2-fluorodecanoic acid **7**: (a) NBS, $Me_3N{\cdot}3HF$, dichloromethane, [95%]; (b) KOAc, DMF, 153°C, [68%]; (c) KOH/methanol, [96%]; (d) Jones oxidation, [67%]

Two principal enzymatic methods are known in the literature to cleave substituted racemic carboxylic acids, the lipase-catalyzed esterification of the acid or hydrolysis of the corresponding ester.[25] We applied both methods to cleave **7**.

2.1. Lipase-catalyzed hydrolysis

Alkyl 2-fluorodecanoates **8**, obtained in the usual way by refluxing acid **7** with the corresponding alcohol in the presence of a catalytic amount of H_2SO_4, have been resolved with moderate enantiomeric excess by the lipases from *Candida antarctica* (CAL, Novozym® 435), *Candida rugosa* (CRL) and *Pseudomonas cepacia* (PCL, Amano PS) (Scheme 3, Table 1). These lipases have also been used successfully for the resolution of other α-branched alkanoic acids.[6,13]

The enantioselective hydrolysis of the esters **8** with the lipases mentioned above has been accomplished in phosphate buffer (c=0.1 mol/l) at pH 7.0 or in distilled water in which the pH 6.0 has been kept constant by a continuous addition of 0.5 molar aqueous NaOH without any co-solvent. The best result (entry 8) was found with the methyl ester **8b** and with PCL as the biocatalyst at pH 6.0.



7 **8a** R = C_2H_5 (*R*)-(-)-**8a** (*S*)-(-)-**7**
7 **8b** R = CH_3 (*R*)-(+)-**8b** (*S*)-(-)-**7**

Scheme 3. Synthesis and lipase-catalyzed resolution of alkyl 2-fluorodecanoates **8**

Table 1
Lipase-catalyzed hydrolysis of alkyl 2-fluorodecanoates **8**

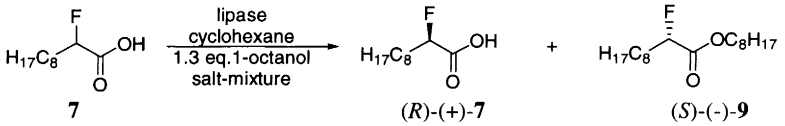
Entry	R	Lipase	Time [h]	Conversion [%]	ee[c] **7** [%]	ee[d] **8** [%]	E	pH
1	C_2H_5	PCL	4.6	75	38	52	3.6	6.0[a]
2	C_2H_5	PCL	4.25	60	22	34	2.0	7.0[a]
3	C_2H_5	CAL	2	55	28	32	2.4	7.0[a]
4	C_2H_5	CRL	1	52	44	49	4.1	7.0[a]
5	CH_3	PCL	1	58	59	65	7.4	7.0[a]
6	CH_3	PCL	0.6	49	77	62	14.4	6.0[a]
7	CH_3	PCL	2.5	52	53	64	6.1	7.0[b]
8	CH_3	CAL	1.6	51	63	52	7.3	6.0[a]
9	CH_3	CRL	0.6	44	47	37	3.9	6.0[a]
10	CH_3	CRL	2.2	26	49	14	1.8	7.0[b]

[a] kept constant by continuous addition of 0.5 M NaOH
[b] kept constant by 0.1 M phosphate buffer
[c] determined by ^{19}F NMR shift experiment [1.3 eq $Eu(hfc)_3$] after esterification with 1-butanol using the DCC/DMAP method[14]
[d] determined by ^{19}F NMR [1.3 eq. of $Eu(hfc)_3$]

2.2. *Lipase-catalyzed esterification*

As shown above, the ee values in the enzymatic hydrolysis of alkyl 2-fluorodecanoates **8** (Table 1) were only moderate. Consequently, we decided to investigate the enzymatic esterification of **7** in order to get higher enantioselectivities. Högberg et al. have shown that lipase-catalyzed esterifications of 2-substituted fatty acids in hydrocarbon solvents occur with better enantiomeric excess than hydrolysis of the corresponding esters.[15] Proper selection of the chain length of the alcohol used led to high *E*-values and yields. Long chain alcohols mostly give higher ees,[16] but at higher concentration these alcohols inhibit the activity of the lipase,[15c,16] whereas short chain alcohols such as ethanol give poor enantioselectivities.[16b,d]

On the other hand, there is no doubt that the most important point in lipase-catalyzed esterification of fatty acid derivatives is the water-activity (a_w) of the reaction mixture. Uncontrolled changes in water-activity before and during the reaction are responsible for variation in the *E*-values and in the rate of the esterification.[16–18] Acknowledging the results from the literature, we decided to use a non-polar solvent, cyclohexane, a small amount of a long chain alcohol (1.3 equiv. 1-octanol), and a constant water-activity. Addition of inorganic salt/salt hydrate mixtures to the reaction medium is known to keep a_w constant, which is necessary to keep catalytic activity and enantioselectivity of the enzyme.[18] The results obtained by esterification of 2-fluorodecanoic acid **7** (Scheme 4) are summarized in Table 2.



7 (*R*)-(+)-**7** (*S*)-(-)-**9**

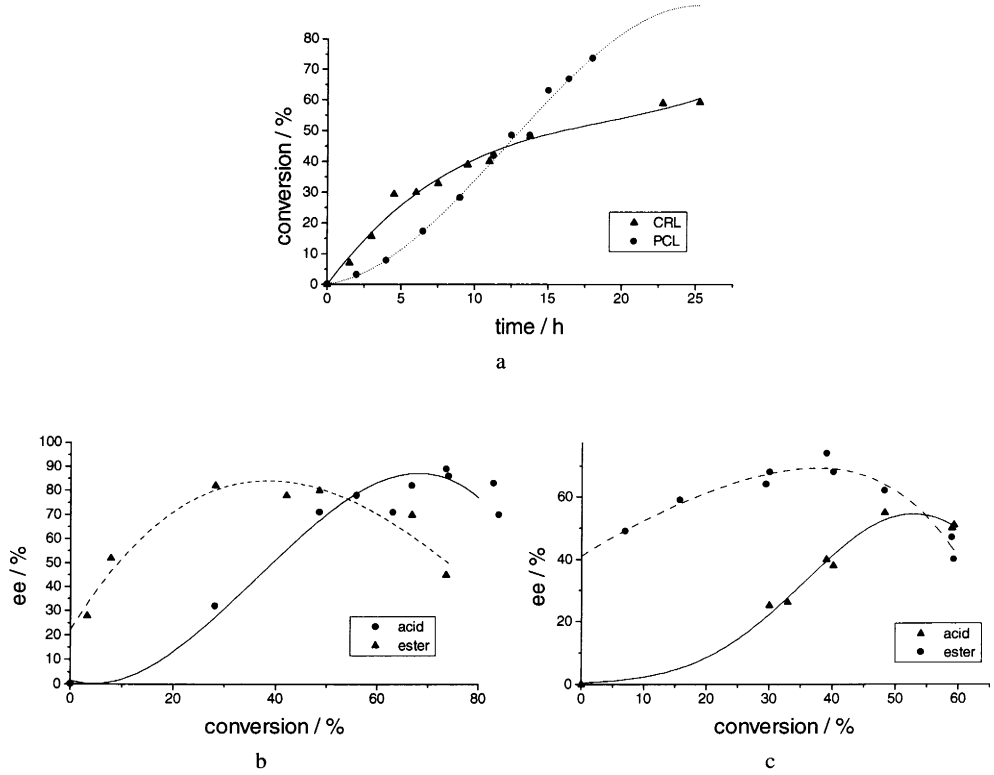
Scheme 4. Lipase-catalyzed esterification of racemic 2-fluorodecanoic acid **7**

Table 2
Enzymatic esterification of 2-fluorodecanoic acid **7** in Table 1

Entry	Lipase	Time [h]	Salt[a]	Conversion	ee[b] **7** [%]	ee[b] **9** [%]	E
1	PCL	12.4	$Na_2SO_4/Na_2SO_4 \cdot 10\ H_2O$	49	71	80	19.0
2	CRL	13.8	$Na_2SO_4/Na_2SO_4 \cdot 10\ H_2O$	48	55	62	7.3

[a] using $Mg(NO_3)_2 \cdot 6H_2O$, $MgCl_2 \cdot 6H_2O$ or KCl the reaction was very slow (nearly 300 h to 50 % conversion) without any enantioselectivity
[b] determined by ^{19}F NMR under the conditions mentioned in table 1

In order to investigate whether the selectivity of the lipase-catalyzed esterification changes during the reaction we measured the conversion and the ee of acid **7** and ester **9** over time. The results are summarized in Scheme 5 and are in agreement with results which were obtained by esterification of 2-methyldecanoic acid under similar conditions.[15,16a,c,17,18k]



Scheme 5. Dependence of conversion and ee values on time for esterification of **7** with 1-octanol. (a) Conversion [%]/time [h] for PCL and CRL reaction (entries 1 and 2, Table 2); (b) ee [%]/conversion [%] for PCL reaction (entry 1, Table 2); (c) ee [%]/conversion [%] for CRL reaction (entry 2, Table 2)

All the used lipases are (*S*)-selective in agreement with the empirical Kazlauskas rule for 2-substituted chiral carboxylic acids and CRL.[19] The absolute configuration of **7** was determined by comparison of the specific rotation with known values.[4d]

3. Experimental

^1H (300 MHz), ^{13}C (75.5 MHz): Bruker WM 300, TMS for ^1H and $CDCl_3$ for ^{13}C NMR as internal

standards. ^{19}F NMR: Bruker WM 300 (282.3 MHz), $CFCl_3$ as internal standard. Mass spectra (electron-impact ionization, 70 eV): GC/MS coupling: Varian GC 3400 MAT and data system of Finnigan/MAT. GC: Hewlett–Packard 5890 II gas chromatograph, quartz capillary column 0.32 mm×30 m, 0.25 μm HP-5 (Hewlett–Packard), nitrogen as carrier gas, and FID. Conversion of the substrates during the enzymatic reactions was determined by GC after silylation with BSA. Optical rotations: Perkin–Elmer 241 polarimeter (Na–D-line: λ=589 nm). Lipase from *Candida rugosa* (CRL) was purchased from Sigma, lipase from *Candida antarctica* (CAL) from Novo Nordisk and lipase *Pseudomonas cepacia* (PCL, Amano PS) was a gift from Amano Pharmaceuticals Co. Phosphate buffer (0.1 M, pH=7.0) was prepared from K_2HPO_4 and KH_2PO_4. Cyclohexane was purified by distillation prior to use.

*3.1. Preparation of 1-bromo-2-fluoro-decane **4***

Compound **3** (14.2 g, 100 mmol) was dissolved in 100 ml of dry dichloromethane and 26.4 g (220 mmol) of $Me_3N \cdot 3HF$ was added. The solution was cooled to 0°C and 21.1 g (120 mmol) of NBS was added in small portions. The reaction mixture was stirred at room temperature for 12 h, poured into ice-water, and a concentrated aqueous NH_3 solution was added up to pH 8–10. Then the phases were separated and the aqueous phase was extracted four times with 150 ml of dichloromethane. The combined organic layers were washed twice with 150 ml of 2N HCl, three times with 150 ml of aqueous $NaHCO_3$ (5%), and dried over $MgSO_4$. Removal of the solvent under reduced pressure led to 22.74 g of a product mixture containing 90% of a 93:7 mixture (GC) of **4** and its regioisomer, 5% (GC) of 1,2-dibromodecane, and 5% of starting material **3** (for the formation of dibromides under the conditions of bromofluorination of alkenes with NBS/$Et_3N \cdot 3HF$, cf.[20]). Spectroscopic data of **4** agree with published values.[21]

*3.2. Preparation of 1-acetoxy-2-fluorodecane **5***

The crude mixture of **4** (22.74 g) was dissolved in 240 ml of DMF. Then 38.0 g (387 mmol) of potassium acetate was added and the mixture was refluxed for 18 h. The reaction mixture was poured into 200 ml of cyclohexane:ethyl acetate (1:1) and extracted six times with water. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was filtered through a short column (3 cm) with silica gel using cyclohexane:ethyl acetate (9:1). Yield: 15.65 g of a mixture containing 90% of **5** and its regioisomer (93:7) and 5% of a diacetate. Spectroscopic data of **5** agree with published values.[4d,22]

*3.3. Preparation of 2-fluorodecan-1-ol **6***

The crude mixture of **5** (15.65 g) was dissolved in 100 ml of methanol and 11.23 g (200 mmol) of KOH was added. The mixture was stirred at room temperature for 18 h, poured into 160 ml of ice-water, and extracted six times with 100 ml of dichloromethane. The combined organic layers were washed three times with 160 ml of water, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Yield: 11.98 g of a mixture of isomers containing nearly 90% of **6** and its regioisomer (93:7). Fp of **6**: 32°C. Spectroscopic data of **6** agree with published values.[4d,22,23]

*3.4. Preparation of 2-fluorodecanoic acid **7***

The crude mixture of **6** was dissolved in 500 ml of acetone and cooled to 0°C. After dropwise addition of 61 ml of Jones-reagent (prepared from 26 g of CrO_3, 23 ml of concentrated H_2SO_4, and 77 ml of

water) the reaction mixture was stirred overnight at room temperature. Then the mixture was cooled to 0°C and 50 ml of isopropanol was added dropwise. Water was added until everything was dissolved and the mixture was extracted five times with 100 ml of dichloromethane. To the combined organic layers 100 ml of saturated aqueous $NaHCO_3$ solution was added and stirred for 10 min, while the sodium salt of **7** precipitated as a white solid. This solid was separated, dissolved in 40 ml of 2N HCl, and extracted three times with 100 ml of dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Yield: 7.98 g (42 mmol) analytically pure **7**. Fp 61°C (cyclohexane) (lit.:[11] Fp 62–65°C, petroleum ether). Spectroscopic data of **7** agree with published values.[4d]

3.5. Preparation of methyl 2-fluorodecanoate **8b**

Compound **7** (4.18 g, 22 mmol), dry methanol (3.52 g, 110 mmol), and 3 ml of concentrated H_2SO_4 were refluxed for 5 h under anhydrous conditions. The reaction mixture was dissolved in 100 ml of water and extracted three times with 50 ml of diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. Distillation under reduced pressure gave 3.51 g (78%) of product **8b**. Bp: 114°C/13 mmHg. ^{1}H NMR: δ 0.88 (t, 3H, $^3J_{H,H}$=6.7 Hz, 10-CH_3), 1.27 (m, 10H, 5-CH_2-9-CH_2), 1.46 (m, 2H, 4-CH_2), 1.88 (m, 2H, 3-CH_2), 3.59 (s, 3H, OCH_3), 4.90 (dt, 1H, $^2J_{H,F}$=49.1 Hz, $^3J_{H,H}$=6.3 Hz, 2-CHF). ^{13}C NMR: δ 14.0 (q, C-10), 22.6, 24.4, 29.1, 29.3, 31.8, 32.6, 32.9 (t, C-3-C-9), 52.2 (q, OCH_3), 89.1 (dd, $^1J_{C,F}$=183.1 Hz, C-2), 170.51 (d, $^2J_{C,F}$=25.4 Hz, C-1). ^{19}F NMR: δ 191.5 (dt, $^2J_{H,F}$=50.4 Hz, $^3J_{H,F}$=25.2 Hz). MS (GC/MS, ion trap): *m/z* (%) 204 (4) [M^+], 161 (21) [$M^+-C_3H_7$], 127 (6) [M^+-HF], 113 (4) [$C_8H_{17}^+$], 105 (23) [$M^+-C_7H_{15}$], 92 (100) [$C_3H_5O_2F$ (McLafferty)], 87 (15), 71 (6) [$C_5H_{11}^+$], 69 (6) [$C_5H_9^+$], 59 (12) [$C_2H_3O_2^+$], 57 (12) [$C_4H_9^+$], 55 (13) [$C_4H_7^+$], 43 (17) [$C_3H_7^+$], 41 (16) [$C_3H_5^+$].

3.6. Preparation of ethyl 2-fluorodecanoate **8a**

Compound **7** (1.90 g, 10 mmol), ethanol (2.30 g, 50 mmol), and 200 mg of concentrated H_2SO_4 were refluxed under anhydrous conditions for 5 h. The reaction mixture was dissolved in 25 ml of water and extracted three times with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. Yield: 1.90 g (87%). Spectroscopic data of **8a** agree with published values.[24]

3.7. General procedure for the lipase-catalyzed hydrolysis of **8** in phosphate buffer

Compound **8** (2 mmol) was suspended in 60 ml of 0.1 M phosphate buffer (pH=7.0) and 10 mg of the enzyme was added. The reaction mixture was stirred at room temperature for the mentioned time (Table 1) and after addition of 10 ml of 2N HCl the mixture was extracted three times with dichloromethane. After GC-analysis to determine conversion, the combined organic layers were extracted three times with saturated $NaHCO_3$. After drying with $MgSO_4$ and evaporation of the solvent under reduced pressure the optically enriched **8** was isolated. An amount of 2N HCl was added to the combined $NaHCO_3$ layers until pH 1–2 was reached and this mixture was extracted twice with dichloromethane. After drying and removal of the solvent the enantiomerically enriched **7** was isolated.

3.8. General procedure for the enzymatic hydrolysis of **8** in distilled water

Compound **8** (2 mmol) was suspended in 50 ml of distilled water and 2 drops of 2 M HCl were added. After that a pre-titration with 0.5 M NaOH was done in order to reach pH 6.0 or 7.0, respectively. Then 10 mg of the enzyme was added and the reaction mixture was stirred at room temperature for the time mentioned in Table 1, while the pH was kept constant by continuous addition of 0.5 M NaOH. The reaction mixture was worked up as mentioned above. $[\alpha]_D^{20}$=+3.84 (*R*)-**8b**, 65% ee, $[\alpha]_D^{20}$=−6.00 (*S*)-**7**, 59% ee (lit.:[4d] $[\alpha]_D^{20}$=−9.7, 86% ee, $[\alpha]_D^{20}$=−2.69 (*R*)-**8a**, 32% ee).

3.9. General procedure for enzymatic esterification of 2-fluorodecanoic acid **7**

Compound **7** (3.00 g, 15.8 mmol) was dissolved in 110 ml of cyclohexane. Then 11.1 mmol of the salt mixture and 2.57 g (19.8 mmol) of 1-octanol were added and the reaction mixture was stirred for 15 min at room temperature in order to get a constant a_w value. Then 789 mg of lipase was added and the conversion was controlled by GC analysis after filtration and silylation. At the end of the reaction the mixture was filtered and extracted five times with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to isolate optically enriched **9**. The combined water layers were acidified with 2 M HCl, and extracted three times with dichloromethane. The combined organic layers were washed with water, dried over $MgSO_4$, and the solvent was removed under reduced pressure in order to isolate enantiomerically enriched **7**. Spectroscopic data of **9**: $[\alpha]_D^{20}$=−4.8 (*S*)-**9**, 24% ee. ^{1}H NMR: δ 0.88 (t, 6H, $^3J_{H,H}$=6.7 Hz, CH_3), 1.28 (m, 20H, CH_2), 1.45 (m, 2H, 4-CH_2), 1.78–1.97 (m, 2H, 3-CH_2), 4.18 (t, 2H, $^3J_{H,H}$=6.7 Hz, CH_2O), 4.87 (dt, 1H, $^2J_{H,F}$=49.4 Hz, $^3J_{H,H}$=6.0 Hz, 2-CHF). ^{13}C NMR: δ 14.0 (t, CH_3), 22.6–32.6 (t, CH_2), 65.5 (t, CH_2O), 89.1 (dt, $^1J_{C,F}$=183.1 Hz, C-2), 170.3 (d, $^2J_{H,F}$=22.9 Hz, C-1). ^{19}F NMR: δ 197.9 (dt, $^2J_{H,F}$=49.6 Hz, $^3J_{H,F}$=24.8 Hz). MS (GC/MS, ion trap), *m/z* (%): 302 (1) [M^+], 259 (0.2) [$M^+-C_3H_7$], 231 (0.2) [$M^+-C_5H_{11}$], 191 (18) [$C_{10}H_{19}O_2F^+$ (McLafferty)], 112 (36) [M^+-190], 97 (5) [$C_7H_{13}^+$], 83 (22) [$C_6H_{11}^+$], 71 (63) [$C_5H_{11}^+$], 69 (24), 57 (100) [$C_4H_9^+$], 55 (37), 43 (85), 41 (50).

Acknowledgements

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