Asymmetric Photodeconjugation: Highly Stereoselective Synthesis of α-Fluorocarboxylic Derivatives

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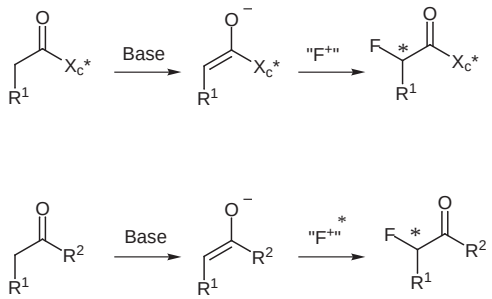
Abstract: Irradiations of α-fluoro-α,β-unsaturated esters lead to the corresponding α-fluoro-β,γ-unsaturated isomers in good yields. The reaction required the use of an achiral base (typically an amine) to promote the protonation of the photodienolic intermediate. By replacing the ethyl group with a diacetone-D-glucose moiety, the reaction can be carried out in a diastereoselective manner to furnish the deconjugated esters with similar yields and selectivities up to 95%. The adducts were submitted to osmylation conditions to deliver α-fluoro-β-hydroxy-butyrolactones in one single step.

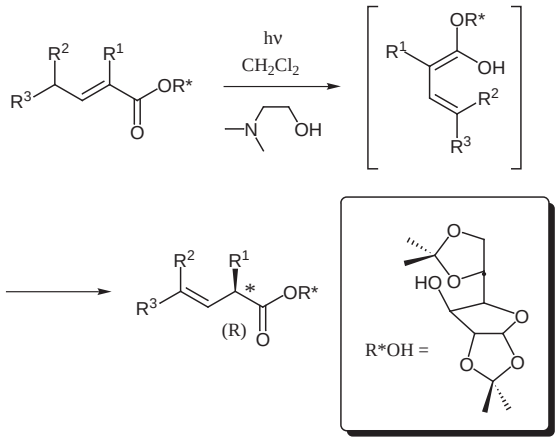
Key words: photochemistry, protonations, asymmetric synthesis, lactones, α-fluoro esters

Due to its strong electronegativity, the presence of one fluorine atom has considerable influence on the biological activities[1] and physical properties of organic molecules. The control of the stereoselectivity of the center bearing the fluorine atom is therefore of considerable interest especially for pharmaceutical compounds.[2] Important achievements have been made for the formation of new C–F bonds starting from carboxylic derivatives[3] and also more recently from enolisable ketones[4] (Scheme 1). This strategy requires the use of stoichiometric *N*-fluorosulfonamides salts and chiral entities, which are usually both expensive.[5]



Scheme 1

As part of our interest for the creation of new stereogenic centers during photochemical processes, we reported a few years ago the possibility to perform highly diastereoselective photodeconjugation of α-alkyl-α,β-unsaturated esters to give the corresponding β,γ-unsaturated isomers (Scheme 2). The formation of the new chiral centre resulted from a stereoselective protonation[6] of one of the two faces of a prochiral dienol.[7] The highest values were obtained by using diacetone D-glucose[8] as chiral alkoxy group.[9] This strategy was successfully applied to the synthesis of natural products, especially pheromones or terpenes by us[10] and more recently by Bach and co-workers. [11]



Scheme 2

In order to generalize this process to other chiral compounds substituted in α position by one halogen atom (R^1 = X), we first tested the photochemical reactivity of unsaturated α-bromo and α-fluoro esters **1** and **2**, easily prepared in few steps according to published procedures (Scheme 3, Table 1).[12–14]

Table 1 Preparation of Ethyl Esters **2**

R^1	R^2	**2**	Yield (%)	(*E*/*Z*)
Me	Me	**a**	88	>98/2
Et	Et	**b**	84	>98/2
-$(CH_2)_5$-		**c**	87	>98/2
n-Octyl	H	**d**	64	>98/2
Et	H	**e**	83	>98/2
i-Pr	H	**f**	68	>98/2
$TBDMSOCH_2$	H	**g**	80	>98/2

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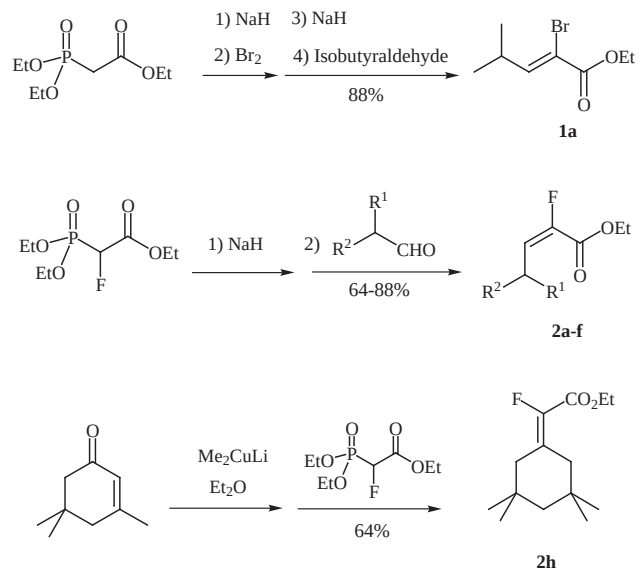


Scheme 3

Under irradiation at 254 nm, ethyl ester **1a** (X = Br) underwent a smooth degradation to reduced compound **3**. In contrast, ethyl ester **2a** (X = F) gave under the same conditions the expected deconjugated isomer **4a** without loss of the fluorine atom (Scheme 4). This difference could be explained by considering the strength of the C–Br and C–F bonds.[15] Furthermore, reductive cleavage of the carbon bromide bond has been already observed for numerous bromo derivatives under photochemical irradiation.[16,17] In order to generalize the photodeconjugation procedure observed with fluoro derivative **2a**, ethyl esters **2b**–**g** were irradiated and afforded the corresponding β,γ-unsaturated isomers **4b**–**g** in similar chemical yields (Table 2).[18]

Table 2 Irradiation of Ethyl Esters **2**

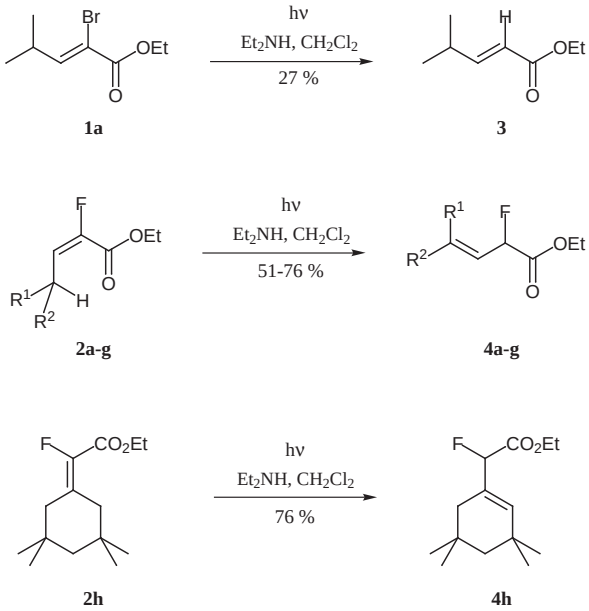
Starting Material **2**	Yield of Product **4** (%)	Ratio
a	51	>98/2
b	74	>98/2
c	83	>98/2
e	74	>98/2
f	55	>98/2
g	76	>98/2

Biographical Sketches

Frédéric Bargiggia was born in Voiron (Isère), France, in 1974. He was a student at the University Joseph Fourier of Grenoble, where he obtained his DEA degree in 1997 in Dr Andrew Greene's Laboratory under the guidance of Prof. Jean-Pierre Depres. He is currently completing his PhD work at the University of Lyon I under the supervision of Prof. Piva, devoted to the synthesis of Amphidinolide (*R*), a complex marine natural product.

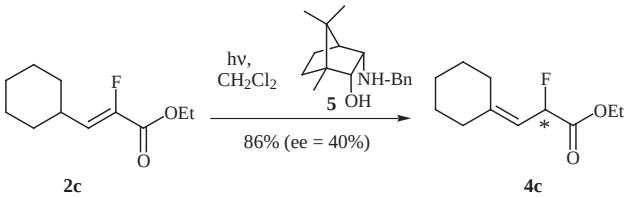
Sylvia Dos Santos was born in Lyon, in 1971. In 1998, she obtained her PhD at the University Claude Bernard Lyon I, working with Dr Agnès Choplin and Prof. Denis Sinou on allylic substitution catalyzed by silica-supported palladium catalysts. In 1999, she was appointed ATER at the same University working in the group of Olivier Piva. Since 2000, she is a teacher in Chambéry.

Olivier Piva was born in Villers-Semeuse (Ardennes) in 1960. He obtained his PhD in 1988 at the University of Reims, under the guidance of Prof. Jean-Pierre Pete. From February 1988 to March 1989, he was a postdoctoral associate with Prof. Dieter Enders at the RWTH in Aachen, working on the SAMP/RAMP hydrazone method. In 1989, he entered the CNRS as Chargé de recherche in Reims and started a new research program on intramolecular [2+2] photocycloadditions. In 1994, he obtained his habilitation and moved for one year to Cambridge University (UK) working with Prof. Steve Ley in the field of total synthesis of natural products. Back to France, he continued to develop his own research in Reims. Since 1998, he is Professor of Chemistry at the University Claude Bernard Lyon I. His research interests include the asymmetric synthesis of natural products, photochemistry and more recently, tandem reactions.



Scheme 4

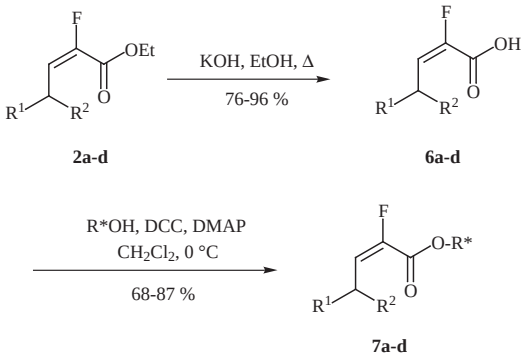
While the deconjugation process appeared efficient with ethyl esters **2**, we decided to study the asymmetric protonation of the prochiral photodienol intermediate. Our enantioselective conditions[6a] were first tested. Ester **2c** was irradiated at 254 nm in dichloromethane at –40 °C in the presence of *N*-benzylaminobornanol **5** (0.15 equivalents). The deconjugation occurred and furnished ester **4c** in 86% yield (Scheme 5). The enantioselectivity was determined from the ^{1}H NMR spectra in the presence of small amounts of Eu(hfc)$_3$ and the selectivity appeared modest (40%).



Scheme 5

It was then decided to turn back to the diastereoselective process by using diacetone D-glucose derivatives. α-Fluoro ethyl esters **2a**–**d** were conveniently saponified to unsaturated acids **6a**–**d** which were esterified[19] with diacetone D-glucose to furnish chiral compounds **7a**–**d** (Scheme 6, Table 3).

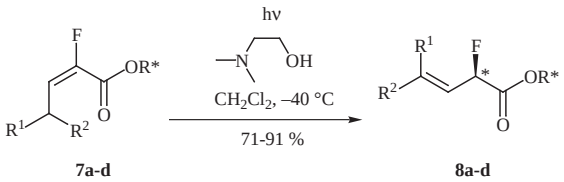
These esters were therefore irradiated at low temperature (–40 °C) in dichloromethane in the presence of one equivalent of dimethylaminoethanol which could act as base as well as proton donor during the reketonization of the prochiral intermediate (Scheme 7).[9] In almost all cases, the selectivity was conveniently determined from the ^{1}H NMR spectra of the crude mixture obtained after irradiation. The α-fluoro-β,γ-unsaturated esters **8a**–**c** were purified by column chromatography, isolated in good yields and also high de (up to 95%). These selectivities are similar to those obtained with α-alkyl-β,γ-unsaturated esters; thus, presence of the fluorine atom seems to have no strong influence on the asymmetric protonation step (Table 4). Despite the presence of the allylic and highly acidic proton on C-2, β,γ-unsaturated isomers were surprisingly stable and could be stored in the refrigerator for months without any alteration or racemization of the new stereogenic center.



Scheme 6

Table 3 Preparation of Diacetone D-Glucose Esters **7**

Ethyl Ester **2**	Yield of Acid **6** (%)	Yield of DAG ester **7** (%)
a	96	68
b	89	83
c	90	87
d	76	77



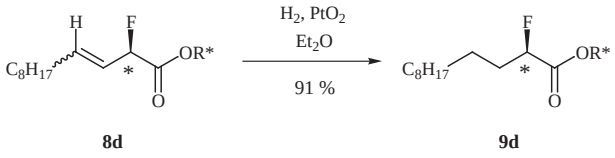
Scheme 7

Table 4 Photodeconjugation of Diacetone D-Glucose Esters **7**

7	Yield of **8** (%)	de (%)[a]	Yield of **9** (%)	de (%)[a]
a	72	88	-	-
b	91	95	-	-
c	74	94	-	-
d	71	-	91	95

[a] Determined from the crude ^{1}H NMR spectra.

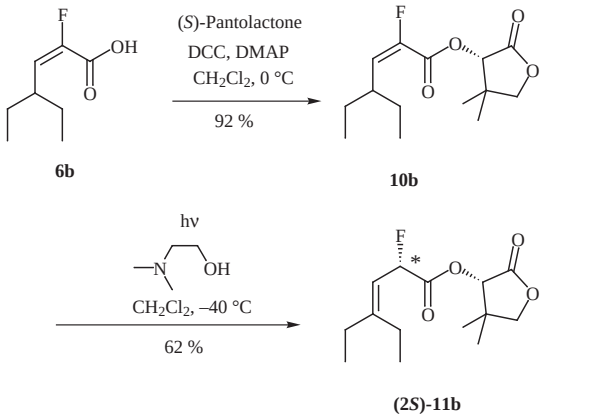
It should be noted that for compound **8d** the presence of the two *E* and *Z* isomers did not allow an easy determination of the diastereoselectivity. To overcome this problem, this ester was efficiently reduced by catalytic hydrogenation of the carbon-carbon double bond over PtO_2[20] without significant cleavage of the C–F bond; the de for the saturated ester **9d** being similar to those of compounds **8a**–**c** (Scheme 8).



8d **9d**

Scheme 8

Furthermore, the attribution of the (*R*) configuration to the new stereogenic C-2 center has been made on the basis of a model, we already proposed to explain the highly selective approach of the aminoalcohol toward one face of the photodienol.[9] Up to date, the main drawback of the photodeconjugation process was the difficulty to prepare esters with opposite configuration on C-2. While L-glucose is not commercially available or needs a multi-step sequence to be prepared, we have however demonstrated that (*S*)-pantolactone can be used for this purpose.[10f] Acid **6b** was therefore esterified with (*S*)-pantolactone to give compound **10b**. By irradiation under the same conditions the deconjugated ester **11b**, for which the (*S*) configuration was assigned, was obtained in convenient yield and selectivity (de = 83%) (Scheme 9).

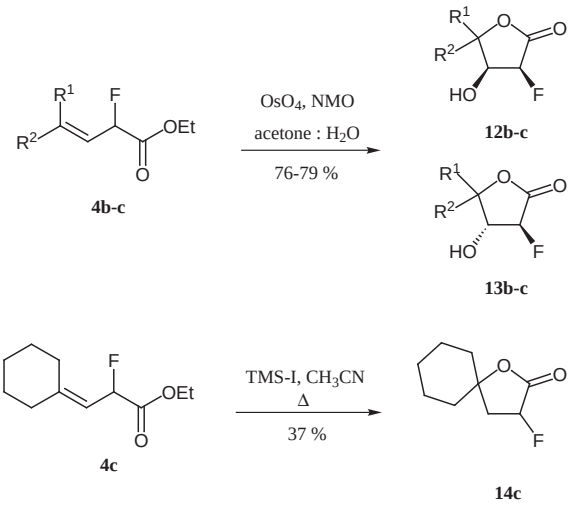


6b **10b**

(2*S*)-11b

Scheme 9

The unsaturation in the acid chain of **4** and **8** potentially allows further transformation into new and more functionalized structures (Scheme 10). For example, esters **4b** and **4c** were submitted to osmylation conditions.[4g,21,22] A direct lactonization of the diol occurred, leading to the formation of α-fluoro-β-hydroxybutyrolactones *syn*-**12b**,**c** and *anti*-**13b**,**c** with a typical 7:3 ratio, easily determined by measurement of coupling constants and comparison with literature data.[23] Finally we noticed the formation of



4b-c **12b-c**

13b-c

4c **14c**

Scheme 10

lactone **14c** by treatment of **4c** with TMS-I[24] but unfortunately in a moderate yield.

In conclusion, we have demonstrated that photodeconjugation can be efficiently performed on α-fluoro-α,β-unsaturated esters. If the alkoxy group is a diacetone-D-glucose moiety, high diastereoselectivities can also be obtained. The α-fluoro- β,γ-unsaturated ethyl esters can also be transformed into α-fluorobutyrolactones according to one single step procedure.

NMR spectra were recorded in $CDCl_3$ using a Bruker AC 250, AC 300 or DRX 500 instrument. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^1H and ^{13}C NMR spectra against internal TMS. FT-IR spectra were measured neat or in $CHCl_3$ on a Perkin Elmer SpectroOne spectrometer. Mass spectra were obtained on a Finigan-MAT 95 XL apparatus. Optical rotations were measured on a Perkin Elmer 243 spectrometer. Flash chromatography was performed on SDS silica gel 60 (40–63 mesh). Solvents were distilled before use according to standard procedures.[25] Other reagents were obtained from commercial sources and used as received. Compound **2h** was prepared according to a literature procedure.[13h]

Ethyl (2*Z*)-2-Bromo-4-methyl-pent-2-enoate (1a)[11a]

To a suspension of NaH (0.48 g, 20 mmol) in Et_2O (200 mL) was added dropwise triethylphosphonoacetate (4.48 g, 20 mmol) at 0 °C. After one hour, Br_2 (3.2g, 20 mmol) was carefully added. The solution was stirred for an additional 3 h. NaH (0.48g, 20 mmol) was added by portion. After 2 h, isobutyraldehyde (1.44g, 20 mmol) in Et_2O (20 mL) was added at r.t. and the resulting solution stirred for 2 h at this temperature. After hydrolysis with brine, the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by distillation under reduced pressure afforded **1a** (3.91g, 17.6 mmol) as a pale yellow liquid (88%).

Bp_{11} 65–67 °C.

IR (neat): 2960, 1700, 1605, 1375, 1220–1195, 1025 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): (*E* isomer) δ = 1.02 (d, 6 H, *J* = 7.0 Hz), 1.33 (t, 3 H, *J* = 7.0 Hz), 3.24 (m, 1 H), 4.26 (q, 2 H, *J* = 7.0 Hz), 6.44 (d, 1 H, *J* = 10.0 Hz); (*Z* isomer) δ = 1.10 (d, 6 H, *J* = 7.0 Hz), 1.33 (t, 3 H, *J* = 7.0 Hz), 3.24 (m, 1 H), 4.26 (q, 2 H, *J* = 7.0 Hz), 7.09 (d, 1 H, *J* = 10.0 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 222 (M^+, 29), 220 (M, 27), 194 (39), 192 (39), 179 (22), 177 (30), 97 (34).

UV (CH_2Cl_2): ε_{229} = 5300; ε_{254} = 760.

Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.45; H, 5.93. Found: C, 43.07; H, 5.83.

Preparation of Ethyl 2-Fluoro-2-alkenoates; Typical Procedure

To a solution of 2-fluoro-triethylphosphonoacetate (2.42g, 10 mmol) in THF (50 mL) was slowly added a hexane solution of *n*-BuLi (1.6 M, 6.6 mL, 10.5 mmol) at 0 °C. The pale yellow solution was stirred for 1 h and then cooled to –20 °C. The aldehyde (10 mmol) in THF (3 mL) was added dropwise to the resulting solution, which was stirred overnight at r.t. Careful hydrolysis was performed with a sat. NH_4Cl solution. Small amounts of H_2O were added in order to dissolve the phosphate salts. After separation of the phases, the aqueous layer was extracted with Et_2O (2 × 50 mL) and the organic phase dried over $MgSO_4$. After filtration and concentration under vacuo, ethyl ester **4** was purified from the crude material by flash chromatography on silica gel (eluent: EtOAc–hexanes, 5:95).

Ethyl (2*E*)-2-Fluoro-4-methylpent-2-enoate (2a)[13d]

Yield: 88%.

IR (film): 2970, 2870, 1730, 1666, 1465, 1315, 1230, 1155 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.05 (d, 6 H, *J* = 6.6 Hz), 1.34 (t, 3 H, *J* = 7.2 Hz), 3.26–3.42 (m, 1 H), 4.27 (q, 2 H, *J* = 7.2 Hz), 5.72 (dd, 1 H, *J* = 10.4, 21.9 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 14.0 (CH_3), 25.3 (CH), 61.2 (OCH_2), 130.0 (d, *J* = 15.5 Hz, CH), 145.8 (d, *J* = 251.8 Hz, C), 161.0 (d, *J* = 35.5 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.2 (d, *J* = 22.3 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 160 (M^+, 1), 153 (5), 140 (15), 125 (100), 115 (53).

Ethyl (2*E*)-4-Ethyl-2-fluorohex-2-enoate (2b)

Yield: 84%.

IR (film): 2970, 1726, 1666, 1560, 1375, 1333, 1275, 1215, 1165, 1110, 1020 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.86 (t, 6 H, *J* = 7.4 Hz), 1.12–1.28 (m, 2 H), 1.34 (t, 3 H, *J* = 7.1 Hz), 1.48–1.60 (m, 2 H), 2.99 (m, 1 H), 4.29 (q, 2 H, *J* = 7.1 Hz), 5.57 (dd, 1 H, *J* = 11.0, 22.7 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 11.5 (CH_3), 14.0 (CH_3), 27.9 (CH_2), 38.7 (d, *J* = 3.4 Hz, CH), 61.2 (CH_2), 127.7 (d, *J* = 15.6 Hz, CH), 147.3 (d, *J* = 250.7 Hz, C), 161.1 (d, *J* = 35.2 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.0 (d, *J* = 22.8 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 188 (M, 21), 160 (32), 159 (18), 132 (84), 113 (62), 85 (44), 70 (100).

UV (CH_2Cl_2): ε_{229} = 7160; ε_{254} = 290.

Anal. Calcd for $C_{10}H_{17}O_2F$: C, 63.80; H, 9.10. Found: C, 64.20; H, 9.47.

Ethyl (2*E*)-3-Cyclohexyl-2-fluoroacrylate (2c)

Yield: 87%.

IR (film): 2920, 2850, 1730, 1666, 1375, 1350, 1300, 1270, 1215, 1180, 1125, 1095 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.08–1.45 (m, 6 H), 1.35 (t, 3 H, *J* = 7.0 Hz), 1.55 (m, 4 H), 3.02 (m, 1 H), 4.27 (q, 2 H, *J* = 7.0 Hz), 5.76 (dd, 1 H, *J* = 10.3, 22.0 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 13.9 (CH_3), 25.2 (CH_2), 25.4 (CH_2), 25.7 (CH_2), 31.9 (CH_2), 34.5 (d, *J* = 3.4 Hz, CH), 61.1 (CH_2), 128.6 (d, *J* = 15 Hz, CH), 145.9 (d, *J* = 251 Hz, C), 160.9 (d, *J* = 36.4 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.2 (d, *J* = 22.8 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 200 (M, 28), 172 (31), 119 (26), 91 (34), 81 (100), 67 (83), 55 (59).

UV (CH_2Cl_2): ε_{236} = 8170; ε_{254} = 415.

Anal. Calcd for $C_{11}H_{17}O_2F$: C, 65.97; H, 8.55. Found: C, 66.29; H, 8.71.

Ethyl (2*E*)-2-Fluorododec-2-enoate (2d)[13e]

Yield: 64%.

IR (film): 2925, 2855, 1730, 1665, 1465, 1375, 1350, 1325, 1225 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (t, 3 H, *J* = 7.5 Hz), 1.22–1.40 (m, 14 H), 1.34 (t, 3 H, *J* = 7.3 Hz), 2.49 (ddt, 2 H, *J* = 6.3, 8.0 Hz), 4.28 (q, 2 H, *J* = 7.3 Hz), 5.91 (dt, 1 H, *J* = 22.0, 8.0 Hz).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.0 (CH_3), 14.1 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 29.2 (CH_2), 29.25 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 61.2 (O-CH_2), 123.7 (d, *J* = 17.7 Hz, CH), 147.0 (d, *J* = 250.4 Hz, C), 161.1 (d, *J* = 36.0 Hz, CO_2R).*

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –123.3 (d, *J* = 17.8 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 245 [(M + 1), 12], 241 (85), 223 (44), 185 (36), 173 (92), 167 (50), 155 (34), 149 (21), 119 (22).

Ethyl (2*E*)-2-Fluorohex-2-enoate (2e)[26]

Yield: 83%.

IR (film): 2960, 2915, 2895, 1730, 1665, 1465, 1405, 1380, 1345, 1280, 1220 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.95 (t, 3 H, *J* = 7.3 Hz), 1.34 (t, 3 H, *J* = 7.2 Hz), 1.41–1.51 (m, 2 H), 2.48 (dt, 2 H, *J* = 8.0, 7.4 Hz), 4.28 (q, 2 H, *J* = 7.2 Hz), 5.90 (dt, 1 H, *J* = 21.8, 8.2 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 13.5 (CH_3), 13.7 (CH_3), 22.4 (CH_2), 27.4 (CH_2), 61.2 (CH_2), 123.4 (d, *J* = 17.7 Hz, CH), 147.1 (d, *J* = 251 Hz, C–F), 161.0 (d, *J* = 35.8 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –123.0 (d, *J* = 22.6 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 160 (M, 2), 131 (12), 110 (16), 85 (32), 71 (100).

Ethyl (2*E*)-2-Fluoro-5-methylhex-2-enoate (2f)[27]

Yield: 68%.

IR (film): 2960, 2870, 1730, 1666, 1465, 1380, 1215, 1155, 1055 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.92 (d, 6 H, *J* = 7.0 Hz), 1.34 (t, 3 H, *J* = 7.0 Hz), 1.72 (m, 1 H), 2.42 (ddd, 2 H, *J* = 1.7, 8.4, 6.9 Hz), 4.29 (q, 2 H, *J* = 7.0 Hz), 5.92 (dt, 1 H, *J* = 22.0, 8.2 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 14.0 (CH_3), 22.1 (CH_3), 28.7 (CH_2), 34.5 (CH), 61.1 (O-CH_2), 122.3 (d, *J* = 17.8 Hz, CH), 147.3 (d, *J* = 250 MHz, C–F), 161.0 (d, *J* = 35.7 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –122.0 (d, *J* = 22.3 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 174 (M, 13), 145 (15), 132 (16, 103 (43), 86 (66), 82 (100).

Ethyl (2*E*)-{[5-*t*-Butyl(dimethyl)silyl]oxy}-2-fluoropent-2-enoate (2g)

Yield: 80%.

IR (film): 2960, 2850, 1730, 1670, 1470, 1395, 1330, 1250, 1220, 1145, 1095 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.34 (t, 3 H, *J* = 7.3 Hz), 2.73 (ddt, 2 H, *J* = 1.7, 6.2, 7.9 Hz), 3.70 (dd, 2 H, *J* = 0.7, 6.1 Hz), 4.29 (q, 2 H, *J* = 7.3 Hz), 6.01 (dt, 1 H, *J* = 21.4, 7.9 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = –5.4 (CH_3), 14.0 (CH_3), 18.2 (C), 25.8 (CH_3), 29.2 (CH_2), 61.2 (CH_2), 61.8 (CH_2), 120.3 (d, *J* = 19.5 Hz, CH), 147.6 (d, *J* = 252 Hz, C), 160.9 (d, *J* = 36.4 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –121.6 (d, *J* = 22.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 277 [(M + 1), 12], 261 (13), 219 (95), 191 (100), 145 (47), 89 (70), 77 (75), 75 (100).

Anal. Calcd for $C_{13}H_{25}O_3FSi$: C, 56.48; H, 9.11. Found: C, 56.72; H, 9.31.

Irradiation of Esters 1 and 2; General Procedure

A solution of ester **1a** (or **2a**–**h**) (10 mmol) and Et_2NH (10 mmol) (100 mL) was poured into quartz tubes and deoxygenated by bubbling with argon. The tubes were placed around a Quartz Dewar containing a short wave length OSRAM lamp. The irradiation was performed at 0–10 °C (external EtOH cooling bath). After disappearance of the starting material (by TLC control), the solvent was removed by concentration. Ester **3** (or **4a**–**h**) was purified by flash chromatography (eluent: EtOAc–pentane, 3:97).

Ethyl (2*E*)-4-Methylpent-2-enoate (3)

Yield: 27% (conversion 64%).

IR (film): 2950, 1695, 1640, 1375, 1360, 1290, 1265, 1140, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.08 (d, 6 H, *J* = 7.0 Hz), 1.30 (t, 3 H, *J* = 7.0 Hz), 2.42 (quint, 1 H, *J* = 7.0 Hz), 4.20 (q, 2 H, *J* = 7.0 Hz), 5.75 (dd, 1 H, *J* = 16, 1.4 Hz), 6.92 (dd, 1 H, *J* = 16, 7.0 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 142 (M, 29), 114 (48), 97 (100), 69 (95).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.57; H, 10.04.

Ethyl 2-Fluoro-4-methylpent-3-enoate (4a)

Yield: 51%.

IR (film): 2965, 2875, 1745, 1660, 1465, 1365, 1285, 1190, 1155 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.29 (t, 3 H, J = 7.1 Hz), 1.79 (s, 3 H), 1.81 (s, 3 H), 4.24 (q, 2 H, J = 7.1 Hz), 5.34 (dd, 1 H, J = 12.1, 9.0 Hz), 5.46 (dd, 1 H, J = 47.3, 9.0 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 14.0 (CH_3), 18.6 (CH_3), 25.8 (CH_3), 60.4 (CH_2), 85.2 (d, *J* = 177.3 Hz, CH), 117.8 (d, *J* = 22.0 Hz, CH=), 142.8 (d, *J* = 12.9 Hz, C=), 169.2 (CO_2R).

^{19}F NMR ($CDCl_3$): δ = –177.9 (d, *J* = 46.5 Hz).

Ethyl 4-Ethyl-2-fluorohex-3-enoate (4b)

Yield: 74%.

IR (film): 2980, 2895, 1745, 1660, 1470, 1360, 1270, 1195, 1125 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.04 (t, 3 H, *J* = 7.3 Hz), 1.06 (t, 3 H, *J* = 7.3 Hz), 1.29 (t, 3 H, *J* = 7.0 Hz), 2.03–2.27 (m, 4 H), 4.24 (q, 2 H, *J* = 7.0 Hz), 5.30 (dd, 1 H, *J* = 9.1, 10.3 Hz), 5.51 (dd, 1 H, *J* = 9.1, 48.6 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 12.0 (CH_3), 13.2 (CH_3), 14.0 (CH_3), 24.2 (CH_2), 29.0 (CH_2), 61.4 (CH_2), 85.0 (d, *J* = 175.8 Hz, CH), 115.7 (d, *J* = 21.0 Hz, CH), 154.6 (d, *J* = 11.9 Hz, C), 169.5 (d, *J* = 27.6 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –177.0 (d, *J* = 44.2 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 189 [(M + 1), 12], 169 (43), 168 (44), 153 (38), 115 (58), 95 (100), 73 (100).

Ethyl 3-Cyclohexylidene-2-fluoropropanoate (4c)

Yield: 83%.

IR (film): 2920, 2860, 1755, 1670, 1630, 1440, 1280, 1190, 1040, 850 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.30 (t, 3 H, *J* = 7.0 Hz), 1.45–1.72 (m, 6 H), 2.05–2.55 (m, 2 H), 2.26–2.40 (m, 2 H), 4.24 (q, 2 H, *J* = 7.1 Hz), 5.29 (ddt, 1 H, *J* = 8.9, 10.2, 1.0 Hz), 5.52 (dd, 1 H, *J* = 8.9, 48.5 Hz).

^{13}C NMR ($CDCl_3$, 62.85 MHz): δ = 14.0 (CH_3), 25.4 (CH_2), 26.3 (CH_2), 27.6 (CH_2), 28.2 (CH_2), 29.7 (CH_2), 61.4 (CH_2), 84.6 (d, *J* = 176 Hz, CH), 114.5 (d, *J* = 21.5 Hz, CH), 151.0 (d, *J* = 10.0 Hz, C), 169.2 (d, *J* = 27 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –177.8 (d, *J* = 54.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 200 (M, 9), 181 (18), 180 (67), 152 (27), 151 (39), 127 (64), 107 (65), 85 (69), 80 (100), 67 (54), 59 (62).

Ethyl (3*Z*)-2-Fluorohex-3-enoate (4e)

Yield: 74% (*E*/*Z* = 70/30).

IR (film): 2980, 1763, 1460, 1370, 1280, 1205, 1035 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): (*E* isomer) δ = 1.03 (t, 3 H, *J* = 7.4 Hz), 1.30 (t, 3 H, *J* = 7.0 Hz), 2.03–2.25 (m, 2 H), 4.26 (q, 2 H, *J* = 7.0 Hz), 5.20 (dd, 1 H, *J* = 3.7, 45.1 Hz), 5.50–5.65 (m, 1 H), 5.95–6.10 (m, 1 H); (*Z* isomer) δ = 1.04 (t, 3 H, *J* = 7.5 Hz), 1.29 (t, 3 H, *J* = 7.1 Hz), 2.15–2.35 (m, 2 H), 4.24 (q, 2 H, *J* = 7.1 Hz), 5.41–5.90 (m, 3 H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): (*E* isomer) δ = 12.6 (CH_3), 13.9 (CH_3), 25.1 (CH_2), 61.5 (OCH_2), 88.6 (d, *J* = 181.1 Hz, C–F), 121.7 (CH), 140.5 (d, *J* = 10.9 Hz, CH), 169.0 (d, *J* = 9.9 Hz, CO_2R). (*Z* isomer) δ = 12.6 (CH_3), 13.6 (CH_3), 21.4 (CH_2), 61.5 (OCH_2), 84.3 (d, *J* = 178 Hz, C–F), 121.3 (CH), 140.2 (d, *J* = 10.5 Hz, CH), 168.6 (d, *J* = 8.3 Hz, CO_2R).

MS (EI, 70 eV): *m*/*z* (%) = 160 (M, 3), 129 (15), 111 (18), 87 (15), 71 (100).

Ethyl (3*E*)-5-{[*t*-Butyl(dimethyl)silyl]oxy}-2-fluoropent-3-enoate (4g)

Yield: 55% (*E*/*Z* = 66/34).

IR (neat): 2960, 2935, 2860, 1769, 1480, 1250, 1115, 1030 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): (*E* and *Z* isomers) δ = 0.05 and 0.06 (s, 6 H), 0.90 (s, 9 H), 1.28 and 1.29 (t, 3 H, *J* = 7.0 Hz), 4.10–4.50 (m, 4 H), 5.30 (ddd, 1 H, *J* = 1.25, 5.8, 42.3 Hz), 5.70–6.10 (m, 2H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): (*E* and *Z* isomers) δ = –5.3 (CH_3), 14.0 (CH_3), 18.3 (C), 25.8 (CH_3), 60.1 (CH_2, *Z* isomer) and 61.6 (CH_2, *E* isomer), 62.3 (OCH_2), 84.6 (d, *J* = 179.2 Hz, CH–F, *Z* isomer) and 88.0 (d, *J* = 183.1 Hz, CH–F, *E* isomer), 121.4 (d, *J* = 19.1 Hz, CH=, *E* isomer) and 121.9 (d, *J* = 22.4 Hz, CH=, *Z* isomer), 135.7 (d, *J* = 10.1 Hz, CH=, *E* isomer) and 137.6 (d, *J* = 8.3 Hz, CH=, *Z* isomer), 168.4 (d, *J* = 28.0 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): (*E* isomer) δ = –185.9 (dd, *J* = 15.3, 48.2 Hz); (*Z* isomer): δ = –182.6 (dd, *J* = 13.9, 35.3 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 277 (M, 46), 275 (25), 257 (75), 219 (38), 211 (33), 173 (62), 145 (100), 97 (100), 63 (27).

Ethyl Fluoro(3,3,5,5-tetramethylcyclohex-1-en-1-yl)acetate (4h)

Yield: 76%.

IR (film): 2948, 2860, 1755, 1455, 1365, 1280, 1205, 1055 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.88 (s, 3 H), 0.96 (s, 3 H), 1.02 (s, 3 H), 1.04 (s, 3 H), 1.27 (d, 1 H, *J* = 7.0 Hz), 1.29 (t, 3H, J = 7.0 Hz), 1.33 (d, 1 H, *J* = 6.4 Hz), 1.64 (d, 1 H, J_{AB} = 16.6 Hz), 1.88 (d, 1 H, J_{AB} = 16.6 Hz), 4.15–4.40 (m, 2 H), 5.13 (d, *J* = 48.5 Hz, 1 H), 5.67 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 14.1 (CH_3), 29.4 (CH_3), 29.7 (CH_3), 30.2 (C^{IV}), 30.8 (CH_3), 31.0 (CH_3), 32.8 (C^{IV}), 36.9 (CH_2), 49.4 (CH_2), 61.4 (CH_2), 92.0 (d, *J* = 182.2 Hz, C–F), 127.9 (d, *J* = 19.2 Hz, C^{IV}), 139.3 (d, *J* = 9.9 Hz), 168.6 (d, *J* = 27.5 Hz, CO_2).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –184.2 (d, *J* = 48.5 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 242 (M, 12), 227 (15), 222 (82), 207 (100), 177 (26), 169 (24), 161 (37), 149 (67), 137 (69), 133 (41), 121 (57), 107 (47).

Saponification of Ethyl Esters (2); Typical Procedure

Ethyl ester **2a**–**d** (20 mmol) diluted in EtOH (5 mL) was added to a solution of KOH (1.68 g, 30 mmol) in EtOH (95mL) and H_2O (5mL). The mixture was heated for 4 h at reflux, cooled to r.t., half-concentrated under vacuum and acidified with 2 N H_2SO_4 solution. After extraction with hexanes, the organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by flash chromatography over silica gel giving acids **6a**–**d**.

(2*E*)-2-Fluoro-4-methylpent-2-enoic Acid (6a)[12b]

Yield: 96%.

IR ($CHCl_3$): 3600–3100, 2970, 2870, 1705, 1655, 1440, 1305, 1240, 1165, 1105 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.01 (d, 6 H, J = 7.0 Hz), 3.29–3.45 (m, 1 H), 5.88 (ddd, 1 H, J = 0.5, 10.7, 21.3 Hz), 10.55–10.90 (m, 1 H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 22.6 (CH_3), 25.5 (CH), 133.0 (d, *J* = 15.1 Hz, CH), 144.9 (d, *J* = 247.3 Hz, C–F), 165.8 (d, *J* = 37.3 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.5 (d, *J* = 22.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 132 (M^+, 8), 117 (65), 91 (59), 87 (100), 69 (75).

(2*E*)-4-Ethyl-2-fluorohex-2-enoic Acid (6b)

Yield: 89%.

IR ($CHCl_3$): 3600–3100, 2960, 2885, 1705, 1655, 1440, 1230, 1115 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.89 (t, 6 H, J = 7.3 Hz), 1.18–1.39 (m, 2 H), 1.45–1.63 (m, 2 H), 2.92–3.13 (m, 1 H), 5.80 (dd, 1 H, J = 11.3, 22.2 Hz), 9.30–9.70 (m, 1 H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 11.5 (CH_3), 27.9 (CH_2), 39.0 (CH), 131.1 (d, *J* = 15.5 Hz, CH), 146.5 (d, *J* = 247 Hz, C–F), 166.2 (d, *J* = 37.5 Hz, CO_2H).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –122.4 (d, *J* = 21.6 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 160 (M^+, 18), 145 (8), 131 (100), 119 (32).

(2*E*)-3-Cyclohexyl-2-fluoroacrylic Acid (6c)

Yield: 90%.

IR (KBr): 3600–3100, 2930, 2850, 1710, 1660, 1440, 1305, 1130, 980 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.05–1.52 (m, 6 H), 1.63–1.85 (m, 4 H), 2.90–3.15 (m, 1 H), 5.91 (dd, 1 H, *J* = 10.5, 21.7 Hz), 7.30–8.00 (m, 1 H).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 25.3 (CH_2), 25.7 (CH_2), 32.7 (CH_2), 34.7 (CH), 131.6 (d, *J* = 15.1 Hz, CH), 144.6 (d, *J* = 250 Hz, C–F), 165.5 (d, *J* = 36.2 Hz, CO_2H).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.1 (d, *J* = 21.1 Hz).

MS (EI, 70 eV): *m*/*z* 172 (M^+, <5), 143 (25), 130 (22), 95 (28), 81 (59), 69 (100).

(2*E*)-2-Fluorododec-2-enoic Acid (6d)

Yield: 76%.

IR ($CHCl_3$): 3600–3000, 2925, 1705, 1650, 1440, 1260, 1115 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (t, 3 H, *J* = 6.2 Hz), 1.15–1.35 (m, 12 H), 1.36–1.48 (m, 2 H), 2.53 (ddt, 1 H, *J* = 1.8, 6.2, 8.1 Hz), 6.07 (dt, 1 H, *J* = 21.3, 8.1 Hz), 6.20–7.20 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.0 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 127.1 (d, *J* = 17.4 Hz, CH), 146.1 (d, *J* = 246 Hz, C–F), 166.3 (d, *J* = 39.1 Hz, CO_2H).

^{19}F NMR ($CDCl_3$, 188.31 MHz): δ = –123.7 (d, *J* = 20.8 Hz).

MS (CI): *m*/*z* (%) = 217 [(M^+ + 1), 100], 195 (5).

Esterification of Acids 6 and Synthesis of Esters 7a–d

To a solution of acid **6** (20 mmol) in CH_2Cl_2 (20 mL) were successively added DMAP (40 mg) and diacetone D-glucose (5.46g, 21 mmol). The solution was cooled at 0 °C with an external ice-water bath. DCC (4.12 g, 20 mmol), first dissolved into CH_2Cl_2 (2 mL), was added dropwise. After 10 min at 0 °C, the cooling bath was removed and the mixture stirred overnight at r.t. Urea was filtered off and the solvent was removed by concentration. Ester **7** was purified by flash chromatography (eluent: EtOAc–hexanes, 10:90).

(2*E*)-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 2-Fluoro-4-methylpent-2-enoate (7a)

Yield: 68%.

$[\alpha]_D^{21}$ –31.0 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2985, 2965, 1743, 1673, 1525, 1455, 1372, 1315, 1255, 1220, 1080, 1025 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.07 (d, 6 H, *J* = 6.7 Hz), 1.30 (s, 3 H), 1.31 (s, 3 H), 1.41 (s, 3 H), 1.53 (s, 3 H), 3.26–3.43 (m, 1 H), 3.98–4.30 (m, 4 H), 4.56 (d, 1 H, *J* = 3.7 Hz), 5.37 (d, 1 H, *J* = 2.4 Hz), 5.80 (dd, 1 H, *J* = 10.5, 21.5 Hz), 5.91 (d, 1 H, *J* = 5.9 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 22.6 (CH_3), 25.0 (CH_3), 25.1 (CH_3), 25.2 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 67.1 (CH_2), 73.4 (CH), 76.9 (CH), 79.7 (CH), 83.1 (CH), 105.0 (CH), 109.2 (C), 112.2 (C), 131.4 (d, *J* = 14.5 Hz, CH), 144.9 (d, *J* = 253.2 Hz, C–F), 159.5 (d, *J* = 36.0 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.7 (d, *J* = 21.9 Hz).

MS (CI): *m*/*z* (%) = 375 [(M^+ + 1), 24], 339 (10), 317 (100), 273 (31), 259 (10), 185 (11).

UV (CH_2Cl_2): ε_{236} = 10300.

Anal. Calcd for $C_{18}H_{27}O_7F$: C, 57.74; H, 7.27. Found: C, 57.27; H, 7.37.

(2*E*)-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 4-Ethyl-2-fluorohex-2-enoate (7b)

Yield: 83%.

$[\alpha]_D^{21}$ –31.0 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2960, 2870, 1745, 1666, 1454, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.87 (t, 3 H, *J* = 7.4 Hz), 0.88 (t, 3 H, *J* = 7.4 Hz), 1.20−1.40 (m, 2 H), 1.30 (s, 3 H), 1.32 (s, 3 H), 1.41 (s, 3 H), 1.45−1.65 (m, 2 H), 1.53 (s, 3 H), 2.90–3.10 (m, 1 H), 3.98–4.28 (m, 4 H), 4.54 (d, 1 H, *J* = 3.7 Hz), 5.40 (d, 1 H, *J* = 2.5 Hz), 5.70 (dd, 1 H, *J* = 11.2, 22.3 Hz), 5.91 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 11.5 (CH_3), 25.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.8 (CH_2), 27.9 (CH_2), 38.3 (CH), 67.2 (CH_2), 72.5 (CH_2), 77.0 (CH_2), 79.8 (CH_2), 83.2 (CH_2), 105.1 (CH), 109.3 (C), 112.4 (C), 129.3 (d, *J* = 14.7 Hz, CH=), 146.6 (d, *J* = 251.9 Hz, C–F), 159.7 (d, *J* = 37.8 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –122.1 (d, *J* = 22.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 402 (M, 1), 388 (40), 387 (100), 329 (22), 269 (20), 243 (16), 185 (15), 143 (32), 127 (34), 113 (70), 101 (100).

Anal. Calcd for $C_{20}H_{31}O_7F$: C, 59.69; H, 7.76. Found: C, 59.73; H, 8.02.

(2*E*)-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 3-Cyclohexyl-2-fluoroprop-2-enoate (7c)

Yield: 87%.

$[\alpha]_D^{21}$ –32.6 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2995, 2935, 2860, 1745, 1666, 1455, 1380, 1305, 1215, 1080, 1030 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.00–1.35 (m, 6 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.38 (s, 3 H), 1.50 (s, 3 H), 1.59–1.80 (m, 4 H), 2.89–3.09 (m, 1 H), 3.96–4.28 (m, 4 H), 4.52 (d, 1 H, *J* = 3.7 Hz), 5.33 (d, 1 H, *J* = 2.1 Hz), 5.79 (dd, 1 H, *J* = 10.4, 21.5 Hz), 5.87 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 25.1 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 26.1 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 32.4 (CH_2), 34.2 (CH), 66.8 (CH_2), 72.4 (CH), 76.9 (CH), 79.3 (CH), 82.8 (CH), 105.0 (CH), 109.3 (C), 112.3 (C), 130.0 (d, *J* = 15.0 Hz, CH), 145.2 (d, *J* = 252.1 Hz, C–F), 159.6 (d, *J* = 36.1 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –125.3 (d, *J* = 22.6 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 414 (M, 1), 399 (55), 341 (7), 281 (9), 255 (6), 155 (14), 135 (12), 127 (18), 113 (54), 101 (100).

UV (CH_2Cl_2): ε_{238} = 9610.

Anal. Calcd for $C_{21}H_{31}O_7F$: C, 60.85; H, 7.54. Found: C, 60.83; H, 7.74.

(2*E*)-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 2-Fluoro-2-dodec-2-enoate (7d)

Yield: 77%.

$[\alpha]_D^{21}$ –26.0 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2980, 2925, 2860, 1735, 1665, 1455, 1375, 1345, 1215, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, 3 H, *J* = 6.0 Hz), 1.15–1.40 (m, 15 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 1.41 (s, 3 H), 1.52 (s, 3 H), 2.46–2.54 (m, 2 H), 3.90–4.30 (m, 4 H), 4.55 (d, 1 H, *J* = 3.7 Hz), 5.36 (d, 1 H, *J* = 2.5 Hz), 5.90 (d, 1 H, *J* = 3.7 Hz), 5.98 (dt, 1 H, *J* = 21.3, 8.1 Hz).

^{13}C NMR ($CDCl_3$, 50.23 MHz): δ = 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 26.2 (CH_3), 26.7 (CH_2), 26.8 (CH_3), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 67.2 (CH_2), 72.5 (CH), 76.9 (CH), 79.7 (CH), 83.2 (CH), 105.1 (CH), 109.3 (C), 112.4 (C), 125.3 (d, *J* = 17.0 Hz, CH), 146.3 (d, *J* = 251 Hz, C–F), 159.7 (d, *J* = 36.1 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 188.31 MHz): δ = –123.7 (d, *J* = 22.0 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 459 [(M^+ + 1), 16], 401 (58), 261 (13), 245 (16), 119 (72), 85 (100), 69 (90).

HMRS: *m*/*z* [M + H^+] calcd for $C_{24}H_{40}O_7F$: 459.2758; found: 459.2759.

UV (CH_2Cl_2): ε_{238} = 9610.

4,4-Dimethyl-2-oxotetrahydrofuran-3-yl (2*E*)-4-Ethyl-2-fluorohex-2-enoate (10b)

Prepared from acid **6b** and (*S*)-(+)-pantolactone according a procedure similar to the synthesis of esters **7a**–**d**. Yield: 92% (*E*/*Z* = 98/2).

$[\alpha]_D^{21}$ –7.7 (*c* 0.1, CH_2Cl_2).

IR ($CHCl_3$): 2970, 2930, 2880, 1800, 1740, 1660, 1460, 1370, 1210, 1150, 1110 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.78 (dd, 1 H, *J* = 22.2, 11.3 Hz), 5.47 (s, 1 H), 4.09 (d, 1 H, *J* = 9.0 Hz), 4.06 (d, 1 H, *J* = 9.0 Hz), 2.99 (dp, 1 H, *J* = 11.3, 2.8 Hz), 1.45–1.64 (m, 2 H), 1.24–1.38 (m, 2 H), 1.25 (s, 3 H), 1.16 (s, 3 H), 1.05 (t, 3 H, *J* = 7.5 Hz), 1.03 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 11.2 (CH_3), 11.3 (CH_3), 19.8 (CH_3), 22.6 (CH_3), 27.6 (2 CH_2), 38.6 (CH), 40.1 (C), 75.6 (CH), 75.9 (CH_2), 129.7 (d, J_{CF} = 15.5 Hz, CH), 146.0 (d, J_{CF} = 250.4 Hz), 159.7 (d, J_{CF} = 37.9 Hz), 171.3 (C).

^{19}F NMR ($CDCl_3$, 282 MHz): δ = – 122.4 (d, *J* = 22.2 Hz).

MS (CI, 70 eV): *m*/*z* (%) = 273 [(M^+ + 1), 100], 161 (4), 115 (12).

HMRS: *m*/*z* [M + H^+] calcd for $C_{14}H_{21}O_4F$: 273.1502; found: 273.1505.

UV (CH_2Cl_2): ε_{240} = 2270.

Irradiation of Diacetone D-Glucose Esters 7a–d and 10b

A solution of esters **7** (or **10**) (2.5 mmol) and *N*,*N*-dimethylaminoethanol (0.22g, 2.5 mmol) in CH_2Cl_2 (250 mL) was poured into quartz tubes. After deoxygenation with argon, the tubes were placed around a quartz Dewar in which was placed a 254 nm wavelength OSRAM lamp. The tubes were cooled at –40 °C and irradiation was performed until complete conversion. After concentration under reduced pressure, the selectivity was determined from ^{1}H NMR spectra of the crude material before any purification. The deconjugated esters **8** (or **11**) were isolated by flash chromatography on silica gel (eluent: EtOAc–hexanes, 15:85).

(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 2-Fluoro-4-methylpent-3-enoate (8a)

Yield: 72% (de = 88%).

$[\alpha]_D^{21}$ –99.6 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2990, 2940, 1770, 1672, 1375, 1265, 1215, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): (major diastereoisomer) δ = 1.29 (s, 3 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 1.81 (s, 3 H), 1.83 (s, 3 H), 3.96–4.21 (m, 4 H), 4.52 (d, 1 H, *J* = 3.7 Hz), 5.32–5.34 (m, 1 H), 5.37 (d, 1 H, *J* = 3.7 Hz), 5.50 (dd, 1 H, *J* = 8.8, 47.8 Hz), 5.90 (d, 1 H, *J* = 3.7 Hz); (minor diastereoisomer, characteristic signal) δ = 4.46 (d, 1 H, *J* = 3.8 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 18.6 (CH_3), 18.7 (CH_3), 25.2 (CH_3), 25.8 (CH_3), 26.2 (CH_3), 26.7(CH_3), 26.8 (CH_3), 67.4 (CH_2), 72.3 (CH_2), 76.7 (CH), 80.0 (CH), 83.1 (CH), 84.9 (d, *J* = 171.2 Hz, CH), 105.1 (CH), 109.4 (C), 112.5 (C), 117.4 (d, *J* = 20.7 Hz, CH=), 144.2 (d, *J* = 10.3 Hz, C=), 168.0 (d, *J* = 28.2 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –178.1 (d, *J* = 53.2 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 374 (M, 8), 360 (18), 359 (100), 113 (18), 101 (55), 87 (32).

HMRS: *m*/*z* calcd for $C_{18}H_{27}O_7F$: 374.1740; found: 374.1742.

(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 4-Ethyl-2-fluorohex-3-enoate (8b)

Yield: 91% (de = 95%).

$[\alpha]_D^{21}$ –96.1 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2985, 1755, 1666, 1465, 1365, 1265, 1215, 1065 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): (major diastereoisomer) δ = 1.04 (t, 3 H, *J* = 7.3 Hz), 1.06 (t, 3 H, *J* = 7.3 Hz), 1.28 (s, 3 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 1.51 (s, 3 H), 2.05–2.22 (m, 4 H), 3.90–4.22 (m, 4 H), 4.51 (d, 1 H, *J* = 3.7 Hz), 5.35 (t, 1 H, *J* = 9.5 Hz), 5.37 (d, 1 H, *J* = 3.7 Hz), 5.52 (dd, 1 H, *J* = 9.5, 48.5 Hz), 5.87 (d, 1 H, *J* = 3.7

Hz); (minor diastereoisomer, characteristic signal) δ = 4.45 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 11.9 (CH_3), 13.3 (CH_3), 24.2 (CH_2), 25.1 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 29.7 (CH_2), 67.2 (CH_2), 72.2 (CH), 76.6 (CH), 80.0 (CH), 83.2 (CH), 84.4 (d, J = 178.4 Hz, CH), 105.1 (CH), 109.3 (C), 112.3 (C), 114.9 (d, *J* = 20.7 Hz, CH=), 154.9 (d, *J* = 9.9 Hz, C=), 167.7 (d, *J* = 28.0 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –176.2 (d, *J* = 46.1 Hz).

MS (EI, 70 eV): *m*/*z* 403 [(M + 1), 11], 388 (26), 387 (81), 367 (29), 185 (19), 123 (26), 113 (59), 101 (100), 85 (28), 73 (63).

(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 3-Cyclohexylidene-2-fluoropropanoate (8c)

Yield: 74% (de = 94%).

$[\alpha]_D^{21}$ – 96.8 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2990, 2940, 2865, 1774, 1674, 1448, 1385, 1260, 1225, 1170, 1085, 1020 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): (major diastereoisomer) δ = 1.29 (s, 3 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 1.55–1.70 (m, 6 H), 2.05–2.22 (m, 2 H), 2.25–2.40 (m, 2 H), 3.95–4.25 (m, 4 H), 4.51 (d, 1 H, *J* = 3.7 Hz, major diastereoisomer), 5.31 (t, 1 H, *J* = 9.2 Hz), 5.38 (d, 1 H, *J* = 2.8 Hz), 5.55 (dd, 1 H, *J* = 9.2, 48.4 Hz), 5.89 (d, 1 H, *J* = 3.7 Hz); (minor diastereoisomer, characteristic signal) δ = 4.46 (d, 1 H, *J* = 3.7 Hz)

^{13}C NMR ($CDCl_3$, 62.85 MHz): δ = 24.7 (CH_3), 25.7 (CH_3), 25.8 (CH_2), 26.3 (CH_3), 27.1 (CH_2), 27.7 (CH_2), 29.2 (CH_2), 36.5 (CH_2), 66.9 (CH_2), 71.7 (CH), 76.1 (CH), 79.9 (CH), 82.9 (CH), 83.6 (d, *J* = 177 Hz, CH), 104.9 (CH), 109.0 (C), 112.0 (C), 113.9 (d, *J* = 20.9 Hz, C), 168.0 (d, *J* = 27.2 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –177.2 (d, *J* = 40.2 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 414 (M, 7), 400 (29), 399 (100), 379 (35), 278 (6), 235 (10), 185 (12), 135 (18), 127 (26), 101 (37).

HMRS: *m*/*z* calcd for $C_{21}H_{31}O_7F$: 414.2053; found: 414.2066.

(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 2-Fluorododec-3-enoate (8d)

Yield: 71%.

IR ($CHCl_3$): 2985, 1772, 1670, 1455, 1375, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): (mixture of *E* and *Z* isomers) δ = 0.87 (t, 3 H, *J* = 6.0 Hz), 1.15–1.35 (m, 15 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 1.90–2.25 (m, 2 H), 3.95–4.30 (m, 4 H), 4.51 (d, 1 H, *J* = 3.7 Hz), 5.22 (dd, 1 H, *J* = 6.6, 47.8 Hz), 5.37 and 5.38 (d, 1 H, *J* = 2.9 Hz), 5.45–6.15 (m, 2 H), 5.90 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR ($CDCl_3$, 62.85 MHz): δ = 14.1 (CH_3), 22.7 (CH_2), 24.2 (CH_2), 25.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 28.5 (CH_2), 28.6 (CH_2), 29.2 (CH_2), 29.25 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 32.3 (CH_2), 32.6 (CH_2), 67.6 (CH_2), 72.4 (CH), 76.8 (CH), 79.9 (CH), 83.3 (CH), 88.7 (d, *J* = 184 Hz, CH), 105.2 (CH), 109.5 (C), 112.5 (C), 121.9 (d, *J* = 19.7 Hz, CH), 139.9 (d, *J* = 10.7 Hz, CH), 168.8 (d, *J* = 24.7 Hz, CO_2R), 167.4 (d, *J* = 13.6 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 188.3 MHz): δ = –180.6, –180.8.

MS (EI, 70 eV): *m*/*z* (%) = 458 (M^+, 2), 443 (86), 187 (7), 101 (100).

HMRS: *m*/*z* calcd for $C_{24}H_{39}O_7F$: 458.2679; found: 458.2676.

4,4-Dimethyl-2-oxotetrahydrofuran-3-yl 4-Ethyl-2-fluorohex-3-enoate (11b)

Yield: 62% (de = 83%).

$[\alpha]_D^{21}$ +63 (*c* 0.1, CH_2Cl_2).

IR ($CHCl_3$): 2970, 2930, 2880, 1790, 1770, 1470, 1380, 1160, 1010 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): (major diastereoisomer) δ = 1.05 (t, 3 H, *J* = 7.7 Hz), 1.06 (t, 3 H, *J* = 7.7 Hz), 1.13 (s, 3 H), 1.24 (s, 3 H), 2.06–2.27 (m, 5 H), 4.03 (d, 1 H, *J* = 9.0 Hz), 4.06 (d, 1 H, *J* = 9.0 Hz), 5.38 (s, 1 H), 5.66 (dd, 1 H, *J* = 48.4, 9.2 Hz); (minor diastereoisomer) δ = 1.05 (t, 3 H, *J* = 7.7 Hz), 1.06 (t, 3 H, *J* = 7.7 Hz), 1.13 (s, 3 H), 1.24 (s, 3 H), 2.06–2.27 (m, 5 H), 4.03 (d, 1 H, *J* = 9.0 Hz), 4.06 (d, 1 H, *J* = 9.0 Hz), 5.43 (s, 1 H), 5.70 (dd, 1 H, *J* = 48.2, 9.6 Hz).

^{13}C NMR ($CDCl_3$, 75.45 MHz): (major diastereoisomer) δ = 12.0 (CH_3), 13.3 (CH_3), 19.7 (CH_3), 22.8 (CH_3), 24.3 (CH_2), 29.0 (CH_2), 40.1 (C), 75.6 (CH), 76.0 (CH_2), 84.5 (d, *J* = 177.6 Hz, CH), 114.9 (d, *J* = 20.7 Hz, CH), 155.6 (d, *J* = 10.4 Hz, C), 168.4 (d, *J* = 28.7 Hz, CO_2R), 171.2 (CO_2R); (minor diastereoisomer) δ = 11.9 (CH_3), 13.2 (CH_3), 19.6 (CH_3), 22.8 (CH_3), 24.2 (CH_2), 28.9 (CH_2), 40.2 (C), 75.5 (CH), 76.0 (CH_2), 84.4 (d, *J* = 178.2 Hz, CH), 115.1 (d, *J* = 20.7 Hz, CH), 155.5 (d, *J* = 10.4 Hz, C), 168.5 (d, *J* = 28.2 Hz, CO_2R), 171.5 (CO_2R).

^{19}F NMR (282 MHz, $CDCl_3$): (major diastereoisomer) δ = –177.2; (minor diastereoisomer) δ = –178.2.

MS (CI, 70 eV): *m*/*z* (%) = 273 [(M^+ + 1), 12], 253 (100).

HMRS: *m*/*z* [M + H^+] calcd for $C_{14}H_{21}O_4F$: 273.1502; found: 273.1231.

UV (CH_2Cl_2): ε_{229} = 860.

(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl) 2-Fluorododecanoate (9d)

Ester **8d** (0.141 g, 0.3 mmol) in Et_2O (5 mL) was placed under H_2 (1 atm) in the presence of a catalytic amount of PtO_2. After 3 h and complete disappearance of the starting material (TLC monitoring), the solution was filtered off over a small pad of celite®. After concentration of the solvent and chromatography on silica gel, ester **9d** was isolated as a pure compound (0.126g).

Yield: 91% (de = 95%).

$[\alpha]_D^{21}$ – 27.4 (*c* 1.0, CH_2Cl_2).

IR ($CHCl_3$): 2985, 2885, 1770, 1455, 1375, 1255, 1215, 1185 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300Hz): (major diastereoisomer: δ = 0.87 (t, 3 H, *J* = 5.9 Hz), 1.15–1.60 (m, 28 H), 1.75–2.00 (m, 2 H), 3.95–4.25 (m, 4 H), 4.52 (d, 1 H, *J* = 3.7 Hz) 4.91 (dt, 1 H, *J* = 48.5, 6.6 Hz), 5.34 (d, 1 H, *J* = 3.0 Hz), 5.89 (d, 1 H, *J* = 3.7 Hz); (minor diastereoisomer, characteristic signal) δ = 4.50 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.0 (CH_3), 22.7 (CH_2), 24.2 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 26.8 (CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 32.2 (CH_2), 32.3 (CH_2), 32.6 (CH_2), 67.6 (CH_2), 72.3 (CH), 76.8 (CH), 80.0 (CH), 83.2 (CH), 88.7 (d, *J* = 184.7 Hz, CH), 105.1 (CH), 109.4 (C), 112.5 (C), 169.0 (d, *J* = 24.7 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 188.31 MHz): δ = –192.4 (dt, *J* = 49.4, 26.7 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 461 [(M^+ + 1), 100], 459 (22), 403 (72), 381 (12), 345 (8).

Osmylation of Esters 4b and 4c

To an acetone–H_2O solution (9:1, 13.5 mL) of ester **4** (2 mmol) was added NMO (4.3 mmol) at 0 °C, followed by a 4% aq soln of OsO_4 (0.4 mL). The resulting mixture was stirred for 8 h. H_2O (2 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered off and concentrated under vacuo. The butyrolactones **12** and **13** were separated and isolated in pure form by flash chromatography on silica gel (eluent: EtOAc–hexanes, 25:75).

(*syn*)-4-Ethyl 2-Fluoro-3-hydroxy-4-hexanolide (12b)
Yield: 54%.

IR ($CHCl_3$): 3600–3250, 2985, 2950, 2885, 1755, 1466, 1280, 1115, 930 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.93–1.03 (m, 6 H), 1.55–1.72 (m, 2 H), 1.91 (t, 1 H, *J* = 7.5 Hz), 1.94 (t, 1 H, *J* = 7.7 Hz), 2.20–2.55 (m, 1 H, OH), 4.31 (d, 1 H, *J* = 4.9 Hz), 5.29 (dd, 1 H, *J* = 4.95, 49.2 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 7.3 ((CH_3), 7.5 (CH_3), 23.2 (CH_2), 27.3 (CH_2), 70.6 (d, *J* = 13.9 Hz, CH), 86.7 (d, *J* = 196.8 Hz, C), 90.8, 170.0 (d, *J* = 22.1 Hz, CO_2).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –215.7 (d, *J* = 48.7 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 177 [(M^+ + 1), 3], 159 (11), 147 (26), 103 (15), 87 (92).

Anal. Calcd for $C_8H_{13}O_3F$: C, 54.54; H, 7.43. Found: C, 54.77; H, 7.63.

(*anti*)-4-Ethyl 2-Fluoro-3-hydroxy-4-hexanolide (13b)
Yield: 22%.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.93–1.00 (m, 6 H), 1.63–1.92 (m, 4 H), 2.80–3.40 (s, 1 H, OH), 4.46 (dd, 1 H, *J* = 7.9, 21.7 Hz), 5.20 (dd, 1 H, *J* = 7.9, 51.6 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 7.35 (CH_3), 7.5 (CH_3), 25.8 (CH_2), 29.9 (CH_2), 76.8 (d, *J* = 19.4 Hz, CH), 88.2 (d, *J* = 8 Hz, C), 91.8 (d, *J* = 193.6 Hz, C–F), 169.2 (d, *J* = 21.4 Hz, CO_2).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ = –202.1 (dd, *J* = 29.5, 52.0 Hz).

MS (CI, 70 eV): *m*/*z* (%) = 177 [(M^+ + 1), 3], 159 (100), 139 (8).

HMRS: *m*/*z* [M + H^+] calcd for $C_8H_{13}O_3F$: 177.0926; found: 177.0928.

(*syn*)-4-Pentamethylene-2-fluoro-3-hydroxybutyrolactone (12c)
Yield: 48%.

IR ($CHCl_3$): 3600−3200, 2985, 2875, 1770, 1465, 1285, 1215 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.42–2.00 (m, 10 H), 2.77 (s, 1 H, OH), 4.34 (d, 1 H, *J* = 4.8 Hz), 5.29 (dd, 1 H, *J* = 4.9, 48.9 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 21.6 (CH_2), 22.3 (CH_2), 24.7 (CH_2), 30.2 (CH_2), 34.7 (CH_2), 70.9 (d, *J* = 14.1 Hz, CH), 86.7 (d, *J* = 198.3 Hz, CH), 87.2 (C), 170.1 (d, *J* = 21.4 Hz, CO_2R).

MS (CI, 70 eV): *m*/*z* (%) = 189 [(M^+ + 1), 10], 171 (100), 151 (85).

HMRS: *m*/*z* [M + H^+] calcd for $C_9H_{13}O_3F$: 189.0927; found: 189.0937.

(*anti*)-4-Pentamethylene-2-fluoro-3-hydroxybutyrolactone (13c)
Yield: 31%.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.50–2.00 (m, 10 H), 2.65–3.15 (m, 1 H, OH), 4.23 (dd, 1 H, *J* = 8.0, 19.5 Hz), 5.17 (dd, 1 H, *J* = 8.0, 51.7 Hz).

^{13}C NMR ($CDCl_3$, 62.89 MHz): δ = 21.1 (CH_2), 21.8 (CH_2), 24.8 (CH_2), 30.6 (CH_2), 35.5 (CH_2), 78.5 (d, *J* = 19.0 Hz, CH), 86.4 (C), 91.3 (d, *J* = 195.0 Hz, C–F), 169.8 (CO_2).

MS (CI, 70 eV): *m*/*z* (%) = 189 [(M^+ + 1), 14], 171 (100), 151 (64).

HMRS: *m*/*z* [M + H^+] calcd for $C_9H_{13}O_3F$: 189.0926; found: 189.0932.

Lactonisation of Ester 4c Induced by TMS-I
To a suspension of anhyd NaI (3 mmol) in freshly distilled CH_3CN (5 mL) was added under argon $(CH_3)_3SiCl$ (3 mmol). The resulting mixture was stirred for 10 min at r.t. Ester **4c** (2.5 mmol) in CH_3CN (1 mL) was added and the solution was heated at 60 °C until complete conversion. After cooling, the solution was hydrolyzed with brine, extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated and product **14c** was purified by flash chromatography.

3-Fluoro-1-oxaspiro[4.5]decan-2-one (14c)
Yield: 37%.

IR ($CHCl_3$): 2938, 2875, 1788, 1455, 1311, 1270, 1220, 1160, 1105 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.40–2.00 (m, 10 H), 2.21 (ddd, 1 H, *J* = 7.0, 13.8, 25.6 Hz), 2.53 (ddd, 1 H, *J* = 8.2, 13.8, 22.1 Hz), 5.24 (ddd, 1 H, *J* = 7.0, 8.2, 51.4 Hz).

^{13}C NMR ($CDCl_3$, 62.85 MHz): δ = 22.2 (CH_2), 22.4 (CH_2), 24.3 (CH_2), 36.9 (CH_2), 37.6 (CH_2), 39.7 (d, *J* = 18.8 Hz, CH_2), 84.6 (C), 86.7 (d, *J* = 188 Hz, CH), 171.0 (d, *J* = 19.5 Hz, CO_2R).

^{19}F NMR ($CDCl_3$, 235.36 MHz): δ =–191.8 (m).

MS (EI, 70 eV): *m*/*z* 173 [(M^+ + 1), 58], 155 (7), 129 (56), 82 (85), 67 (61).

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