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ETHYL PHENYLSULFINYL FLUOROACETATE, A NEW AND VERSATILE REAGENT FOR THE PREPARATION OF α-FLUORO-α,β-UNSATURATED CARBOXYLIC ACID ESTERS

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Summary: The title compound **2** can be alkylated with a wide range of alkyl halides and Michael acceptors. Subsequent thermal elimination of phenyl sulfinic acid **3** leads to α-fluoro-α,β-unsaturated ethyl carboxylates **5** and **10**, an important class of intermediates for fluorine containing biologically active compounds.

α-Fluoro-α,β-unsaturated carbonyl compounds are important intermediates for the preparation of fluorine containing biologically active compounds like pheromoneanalogues,[2,3] 5-fluoroarachidonic acid,[4] retinoids [5-7] and fluoroolefin dipeptide isosteres.[8-10] Methods for their (in particular stereoselective) preparation, are therefore useful. Table 1 summarizes the most selective procedures known thus far,[11] including a new method which is the subject of this paper.

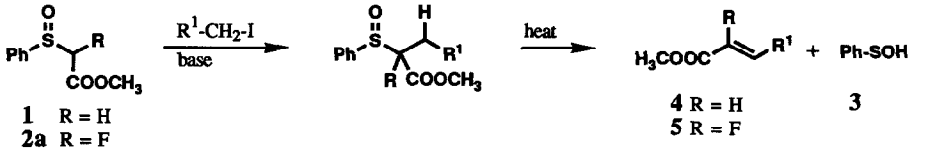
Table 1: α-Fluoro-α,β-unsaturated Carbonyl Compounds

Entry	Reagent	Substrate	Cond	X-CO-CF=CH-R Z/E-ratio	X	Ref
1	:CClF	EtO-CH=CH-R	a	100.0	H	2,12
2	$EtOOC\text{-}CHF\text{-}PO(OEt)_2$	OHC-R	b	<10:90	OEt	5,13,14
3	$F_2C{=}CF\text{-}Li$	OHC-R	c	100:0	OR'	15
4	$MeOOC\text{-}CCl_2F$	OHC-R	d	>90:10	OMe	16
5	PhSO-CHF-COOEt	$Br\text{-}CH_2\text{-}R$	e	>95:5	OEt	-

(a). 1) $CHCl_2F$, 60% KOH, 18-crown-6, 2) water, reflux; (b). LDA, -70°; (c).1) $CF_2{=}CFCl$, sec. BuLi, ether, -60°, 2) conc sulfuric acid, 3) R'OH, (d). Zn-Cu, Ac_2O, THF, 50°; (e). 1) base, solvent, 2) heat.

Schlosser described the solvolytic ring opening of chlorofluorocyclopropyl ethers, adducts of chlorofluoro carbene with various enolethers, to give exclusively the Z-configurated aldehydes (entry 1). Electron withdrawing substituents in R slow down or prevent this ring opening [8] Phosphono fluoroacetates react with aldehydes in a Horner-Emmons reaction to give predominantly the E-products (entry 2) This is still the only method showing this selectivity. The addition of lithio trifluoro-ethene to aldehydes (entry 3) provides trifluoro allylalcohols. These compounds upon treatment with concentrated sulfuric acid rearrange to (Z)-α-fluoro-α,β-unsaturated carboxylic acid fluorides, precursors of the corresponding acids, esters and amides. Clearly these conditions exclude any sensitive functionalities in the molecule. Therefore, the Reformatzky-type reaction of aldehydes with methyl dichlorofluoroacetate in the presence of acetic anhydride and excess zinc (entry 4) is in many instances the method of choice for the preparation of Z-configurated α-fluoro-α,β-unsaturated esters with sensitive functionality which may be necessary for further elaboration of the product.[10,16] In this paper, we describe a new method (entry 5) in which alkyl halides and Michael acceptors are fluoroolefinated to α-fluoro-α,β-unsaturated ethyl carboxylates.

Trost and others have described the alkylation of methyl α-phenylsulfinyl acetate **1** and similar compounds by alkyl halides [17-21] and methyl acrylate.[21-23] In a subsequent step (generally performed in one pot) the thermal elimination of phenylsulfinic acid **3** leads to the formation of unsaturated esters **4**. To obtain α-fluorinated compounds **5** by an analogous pathway, we use the α-fluorinated arylsulfinyl acetates **2** as reagents. These reagents and their application have not been previously reported.



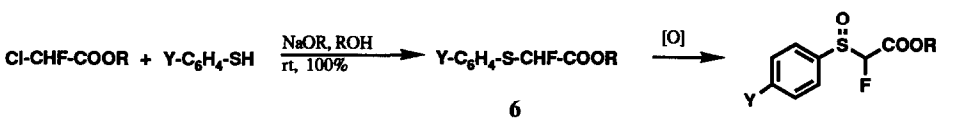
1 R = H
2a R = F

4 R = H
5 R = F

3

Results and Discussion

Preparation of 2 and evaluation of reaction conditions. Starting materials **2** may be readily obtained from the reaction of the appropriate sodium thiophenolate with methyl or ethyl chlorofluoroacetate in alcoholic solution to provide in the first instance **6** [24] which is then further oxidized When sodium metaperiodate is used as the oxidant in aqueous alcohol over oxidation to the known sulfone occurs [26,27]. This may be rectified by utilizing percarboxylic acids at low temperature thus leading to the novel sulfoxides **2** only.



6

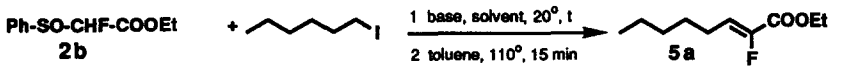
2	**a**	**b**	**c**	**d**
Y	H	H	Cl	OMe
R	Me	Et	Et	Et

To find optimal conditions for the alkylative elimination, we treated solutions of **2b** (2 mmol) in 3 ml of different solvents with various bases (2.2 mmol) and 1-iodohexane (3 mmol). After complete conversion and aqueous workup, the crude alkylation product was refluxed in toluene for 15 minutes to eliminate phenylsulfinic acid. The isolated yields of ethyl 2-fluoro-2(Z)-octenoate **5a** are indicated in table 2.

A wide variety of base/solvent combinations can effectively be used to deprotonate **2b**. The reaction time for the subsequent alkylation with 1-iodohexane is not surprisingly dependent on the solvent with dipolar aprotic N,N-dimethylformamide and acetonitrile being the best in this respect. However, even less polar and less toxic solvents like dichloromethane, ethylmethyl ketone, dimethoxyethane (or THF, not shown), ethyl acetate or toluene may be used for this purpose The thermal cis-elimination (vide infra) affords the final product **5a** and phenylsulfinic acid which readily disproportionates to phenyl benzenethiosulfonate and diphenyl disulfide [28, 29]

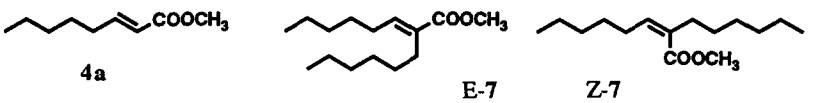
The ease with which this reaction sequence occured prompted us to re-investigate the non-fluorinated series, as **1** is reported to react only sluggishly with alkyl halides .[17] In contrast to this report, **1** turned out to be extremely reactive (table 2, entry 11) and gave a mixture of mono- and bisalkylation products leading to **4a** (E/Z = 95:5) and **7** (E/Z = 88:12) after elimination An 85 % yield of **7** was obtained when **1** was alkylated with excess iodohexane and base (2 5 equivalents, DMF, 5 minutes) and the product was refluxed in toluene for 5 minutes

Table 2:



Entry	Base	Solvent	Time t [h]	Yield [%]	Comments
1	NaH	DMF	1	73	1.1 eq. iodohexane
2	NaOEt	DMF	0.4	74	-
3	K_2CO_3	DMF	24	68	3 eq. base, PTC-cat. no effect on t, a)
4	BDDDP	DMF	0 5	85	"Schwesinger-base" b)
5	BDDDP	CH_3CN	0.5	83	-
6	BDDDP	CH_2Cl_2	5	88	-
7	BDDDP	Et-CO-Me	6	86	-
8	BDDDP	MeCOOEt	24	51	conversion 75%, yield not corrected
9	BDDDP	DME	28	58	-
10	BDDDP	toluene	30	68	1.36 eq. iodohexane
11	**1**, NaH	DMF	0.2	55	**4a** [+ **7** (14%)]

a) 18-crown-6 and TDA-1 [30] have been tried;
b) 2-tert.-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine [31]



Sope and limitations. Using standard conditions (NaH, DMF, 0-20°C) we alkylated **2b, c** and **d** with a variety of alkyl halides and sulfonates Without isolating the intermediates we induced elimination by just heating the solution to 95° for one hour to get after workup and chromatography the products indicated in table 3. Some general remarks are outlined below.

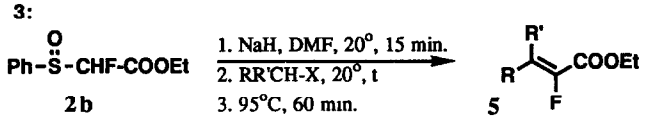
Leaving group and branching of the alkylating agent The reaction time and yields are dependent on the reactivity of the alkylating agent It is therefore not surprising that the reaction is best conducted with iodides and bromides rather than chlorides (entry 1 and 3). The usually reactive sulfonates gave low yields of the products (entry 2 and 14) This has been shown in other C-C bond forming reactions [32] Sterically hindered alkyl halides, for example neopentyl iodide and neophyl chloride (Ph-CMe_2-CH_2Cl), do not react under these conditions, similar to the reaction with other nucleophiles.[33,34] Secondary bromides react sluggishly (entry 5) unless they are activated by an ester group in the α-position (entry 6) and gave mixtures of E- and Z-isomers in the case where R and R' are different.

Functional groups . Many functional groups are found to be compatible with the conditions of this alkylative elimination reaction (see table 3): esters (entry 6-9, 15), acetales (10, 11, 14), silyl ethers (12, 13), imides and amides (16-18). However halides and sulfonates with β-heterosubstituents are known to exhibit low reactivity [35-37] Therefore compounds of this kind, as for the starting materials in entry 10, 12, 16 and 18, require longer reaction times and give comparable low yields under the standard conditions. On the other hand by using the more polar HMPA instead of DMF as the solvent the yields for these reactions are increased substantially (see entry 3, 10, 16, and 18, b) Since α-chiral aldehydes are known to racemize easily under the conditions of a Reformatzky reaction,[38]products like **5b** and **5o** are difficult to obtain in optically pure form by the Ishihara procedure.[16] Our new method utilizing the optically stable alkyl halides in entry 2 and 14 is therefore of special interest, **5o** and similar compounds are used to prepare fluoroolefin dipeptide isosteres.[8,10]

Reagent: p-Chloro and p-methoxy substituents in the aromatic ring of **2b** (**2c** and **2d**) do not alter the reactivity and yield (see entry 3, a). During the reaction of the methylester **2a** with 1-iodobutane and the 3-silyloxy bromopropane (see entry 13) using the one pot procedure (alkylation in DMF, 20°, subsequent elimination by heating), substantial amounts of

the corresponding butyl- and 3-silyloxypropylesters **8** and **9** respectively are formed. This may be due to the saponification of the initially formed methylesters with sodium halide and subsequent alkylation with excess substrate. By using the ethylesters **2b-d** or the two step procedure this side reaction can be avoided

Table 3:



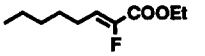
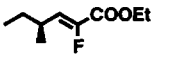
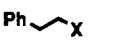
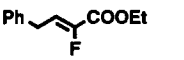
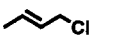
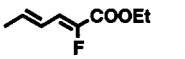
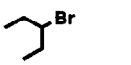
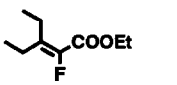
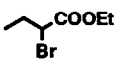
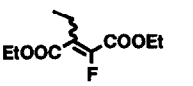
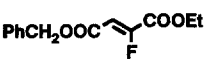
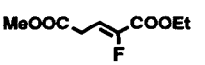
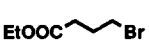
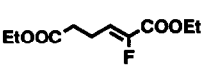
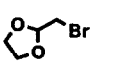
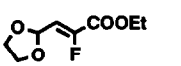
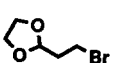
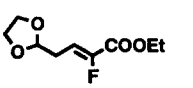
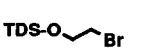
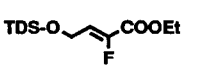
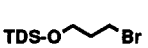
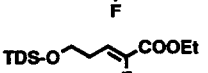
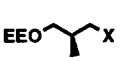
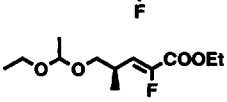
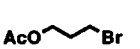
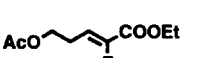
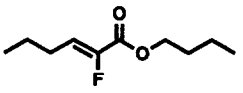
Entry	RR'CH-X	X	Time [h]	Yield [%]	Product
1		Cl Br I	3 0.75 1	44 77 73	 **5a**
2		Br OMs	3 24	64 43	 **5b**
3		Cl Br Cl	5 1 7.5	24 76,80,81 a) 69 b)	 **5c**
4			1	70	 **5d**
5			4	28	 **5e**
6			1	56	 **5f**
7			1	28	 **5g**
8			2	24	 **5h**
9			2	85	 **5i**
10			21 22	28 76 b)	 **5k**
11			1 5	63	 **5l**
12			2	44	 **5m**
13			1	70	 **5n**
14		Br OTs	3 3	61 20	 **5o**
15			1	47	 **5p**

Table 3: continued

Entry	RR'CH-X	Time [h]	Yield [%]	Product	
16	PhthN–Br	1 1	39 63 b)	PhthN–C(F)=C–COOEt	**5q**
17	PhthN–Br	1	73	PhthN–C(F)=C–COOEt	**5r**
18	BOC–N(H)–Br	5 0.5	18 90 b)	BOC–N(H)–C(F)=C–COOEt	**5s**

a) using **2b**, **2c** and **2d** respectively; b) HMPA instead of DMF, isolation of the crude intermediate, refluxing in toluene.



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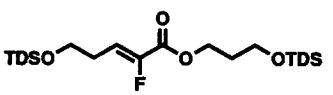
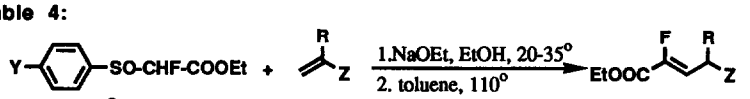


9

Alkylation with Michael acceptors. The low yield observed with methyl 3-bromopropionate (entry 8) is due to the competing elimination of HBr to afford methyl acrylate. This may be overcome by using an acrylate ester itself or other Michael acceptors as alkylating agents for **2b,c,d**. The reaction with such olefins was best carried out in ethanol using catalytic amounts of sodium ethoxide. Elimination as described before gave the final products **10** shown in table 4. Only methyl methacrylate and ethyl N-acetyl dehydroalanine (entry 3 and 5) are poor substrates under these conditions affording the products **10c** and **10e** in lower yield. A further problem is the formation of the double bond isomer **11**. In all other cases the stabilizing effect of fluorine to the double bond [39] is predominant. This may be demonstrated by attempted isomerisation of

Table 4:

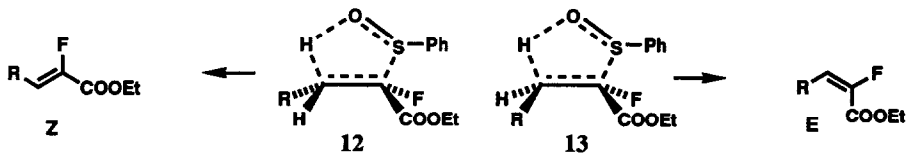


2 **10**

Entry	Y	R	Z	Yield [%]	Product	
1	Cl	H	COOEt	81	EtOOC(F)=C–COOEt	**10a**
2	OCH_3	H	CN	45	EtOOC(F)=C–CN	**10b**
3	H	CH_3	COOEt	30	EtOOC(F)=C(CH_3)–COOEt	**10c**
4	OCH_3	H	CO-Et	70	EtOOC(F)=C–C(=O)–Et	**10d**
5	OCH_3	NHAc	COOEt	34	EtOOC(F)=C(NHAc)–COOEt	**10e**
					EtOOC(F)=C(NHAc)–COOEt	**11**

10a which was impossible under either equilibrium conditions (cat. NaOEt, EtOH) or even by protonation and deuteration of the anion formed with LDA .[8]

The stereoselectivity of the sulfoxide elimination. The products listed in tables 2-4 exhibit a high Z/E product ratio of 95:5 or better, similar to that in the non-fluorinated series. The only exception is the reaction with benzyl bromoacetate (entry 7) furnishing the fluorofumaric acid derivative along with its isomer in a ratio of 83:17. As Trost has already shown for the non fluorinated compounds,[40] these results can be rationalized by the geometry of the transition states **12** and **13** leading to Z and E products respectively. Thus steric repulsion of R and COOEt in transition state **13** causes its energy to be higher compared to that of **12**. In the case of R = COOBzl a dipole interaction of R and F would somewhat destabilize **12** thus resulting in a slightly lower selectivity.



We found that Ishihara's Reformatzky procedure (see table 1, entry 4) give α-fluoro-α,β-unsaturated esters with variable Z/E-ratio depending on the substrate. Usually around 90:10 it drops to 60:40 with phthaloyl protected glycinal as substrate (see table 5) .

Table 5: Preparation of **PhthN-CH_2-CH=CF-COOR 5q**, comparison of the stereoselectivity utilizing different methods.

Substrate	Reagent	Conditions	Yield [%]	R	Z/E ratio
PhthN-CH_2-CHO	Cl_2CF-$COOCH_3$	Zn, CuCl, THF rfl, Ac_2O	53	Me	75:25
"	"	" TFAA[a]	42	Me	60:40
PhthN-CH_2CH_2-Br	PhSO-CHF-COOEt	1. NaH, HMPA, rt 2. toluene, rfl	63	Et	96:4

[a] the use of trifluoroacetic acid anhydride (TFAA) instead of acetic anhydride to achieve acylation and reductive elimination of the intermediate is a variation of the reported method,[16] shown by us to shorten the reaction time, usually without effect on the selectivity .[10]

Conclusion.

We have established a new procedure for the preparation of α-fluoro-α,β-unsaturated carboxylic acid esters. The reagent, ethyl phenylsulfinyl fluoroacetate, is easily prepared from commercial starting materials and can be alkylated with a wide variety of alkyl halides and Michael acceptors The subsequent thermal elimination of phenylsulfinic acid (either in a one pot procedure or after workup) furnishes the final products. When compared to known methods (see table 1) it exhibits some advantages For the first time easy accesible and (optically) stable alkyl halides can be used for the two carbon elongation instead of aldehydes or aldehyde derivatives The reaction conditions allow the presence of many functional groups, even amides with free NH. In contrast, Ishihara's procedure[41] with amino aldehydes lead to complex mixtures. The

stereoselectivity starting with primary substrates is constantly high and not dependent on the substituents present in the molecule. Only sterically hindered neopentyl like alkyl halides do not react with the reagent. Since α-fluoro-α,β-unsaturated carbonyl compounds are useful intermediates in fluoroorganic chemistry this new general method should find further applications.

EXPERIMENTAL

General. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and were used without further purification. Flash chromatography (FC) following the method described by Still[42] was performed with Merck silica gel 60 (230-400 mesh ASTM). Boiling points (bp) are uncorrected. IR (ν [cm^{-1}]): Perkin -Elmer IR 298 (in solution using dichloromethane). ^1H NMR (δ [ppm] relative to internal TMS; in $CDCl_3$; J [Hz] = apparent coupling constant): Bruker WM 250 MS: Varian CH-7 MAT and CEC 21/100, at 70 eV.

Alkyl α-arylthio-α-fluoroacetate **(6)**, *general procedure.* The solution of 0.11 mol sodium in 100 ml of the appropriate alkohol was treated with 0.1 mol of the (substituted) thiophenol followed by 0.13 mol alkyl chlorofluoroacetate.[43] After stirring for 30 minutes at room temperature the formation of **6** was complete and ready for oxidation in situ using sodium metaperiodate (see below) Alternatively the mixture was diluted with 250 ml pentane/ether (1:1), washed three times with water, dried and evaporated to give **6** in quantitative yield Distillation is possible but not necessary. Compounds **6** decompose slowly on standing at room temperature

6a, Ph-S-CHF-COOMe. bp = 75°C/0.04 mbar; ^1H NMR (60 MHz): 3 55 (s, 3H), 5.93 (d, 50.4 Hz, CHF), 7-7.4 (m, 5H); **6c**, Cl-C_6H_4-S-CHF-COOEt. bp = 90-92°C/0 02 mbar; ^1H NMR: 1.21 (t, 3H), 4.15 (q, 2H), 6.02 (d, 51 Hz, CHF), 7.33 and 7.48 (AA'BB', 4H); MS: 248, 250 (M^+); **6d**, MeO-C_6H_4-S-CHF-COOEt: IR - 1750 (CO), 1590, 1490, 1245, 1175, 1030, 835; ^1H NMR. 1.20, (t, 3H), 3.82 (s, 3H), 4.14 (q, 2H), 5.98 (d, 52 Hz, CHF), 6.88 and 7.49 (AA'BB', 4H); MS: 244 (M^+), 171 (M - COOEt), 139 (100%, MeO-C_6H_4-S^+).

Alkyl α-arylsulfinyl-α-fluoroacetate **(2)**, *general procedure A.* The solution of 0.1 mol **6** in 100 ml of the appropriate alkohol (this can be the solution of crude material before workup) was treated with 22 g (0.1 mol) sodium metaperiodate and 40 ml water and heated to 60°C for 2 days. After filtration the filtrate was evaporated to dryness. The residue was dissolved in ether and dried over sodium sulfate. Removal of the solvent and FC on silica gel using hexane/ethyl acetate mixtures as eluent gave (eluting in the following order) unreacted starting material **6**, alkyl arylsulfonyl fluoroacetate (the corresponding sulfone) and the sulfoxide **2** (yield below 50%).

General procedure B: A solution of 0 1 mol **6** in 200 ml dichloromethane was treated with a solution of 24 g 3-chloro perbenzoic acid (85%, 0.12 mol) in 200 ml dichloromethane at -60°C and stirred overnight. After warming to room temperature the mixture was filtered and the filtrate washed with aqueous sodium bicarbonate and ammonium chloride Drying, evaporation and FC of the residue furnished compounds **2** in 80% yield. Compounds **2** are mixtures of diastereomers due to asymmetric centres on sulfur and carbon.

2a, Ph-SO-CHF-COOMe: ^1H NMR: 3.75 (s, 3H, OCH_3), 5.52 and 5.70 (two d, J = 46 and 48 Hz, respectively, 1H, CH-F); 7.5-7.7 (m, 5H, C_6H_5) MS: 216 (M^+); 125 (100%, PhSO); **2b**, Ph-SO-CHF-COOEt: ^1H NMR, diastereomer I: 1.11 (t, 7Hz, 3H, O-C-CH_3); 4.04 (q, 7Hz, 2H, OCH_2); 5.71 (d, 48Hz, CHF); 7.5 (br. s); diastereomer II: 1.18 (t), 4.09 (q), 5,53 (d, 46Hz); 7.5 (br. s). A small sample was distilled at 112°C/0.06 mbar; **2c**, Cl-C_6H_4-SO-CHF-COOEt: ^1H NMR: 1.27 (t), 4.23 (q), 5.49 and 5.69

(doubletts, 47.5 and 49.5 Hz), 7.5-7.65 (m); MS-FD: 264, 266 (M^+), **2d**, MeO-C_6H_4-SO-CHF-COOEt: ^1H NMR: 1.1-1.25 (m), 3 85 (s, OCH_3), 4 21 (q, OCH_2), 5 44 and 5.66 (d, 49 and 50 Hz, CHF), 7.07-7.12 (m, 2H), 7.58-7.63 (m, 2H); MS: 260 (M^+).

Ethyl 2-fluoro-2(Z)-octenoate **(5a)**, *general procedure* (see table 2) A solution of **2b** (2 mmol) in 3 ml of a suitable solvent was treated with 2.2 mmol of a base and 3 mmol of 1-iodohexane. The mixture was stirred at room temp. for the time indicated in table 2, poured on aqueous ammonium chloride solution and extracted with ethyl acetate/hexane (1:1). After drying and evaporation the residue was dissolved in 10 ml of toluene and refluxed for 15 min. Subsequent evaporation and FC on 50 g silica gel using hexane first and hexane/ethyl acetate (10 1) as eluents gave ethyl 2-fluoro-2(Z)octenoate **5a**.

Ethyl 2-fluoro-2-alkenoates **(5a-s)**, *general procedure* (see table 3). A suspension of 0.33 g sodium hydride (80% in oil, 11 mmol) in 10 ml dry DMF was cooled to 0°C under argon and treated with a solution of 10 mmol ethyl arylsulfinyl fluoroacetates (**2b-d**) in 4 ml DMF After stirring at room temperature for 20 minutes the mixture was cooled to 5°C and 11 mmol of the alkylating agent was added in one portion. The reaction mixture was stirred at room temperature for the time indicated in the table The mixture was then heated to 95°C for one hour, poured on ice/aqueous ammonium chloride and extracted with hexane/ethyl acetate. Drying, evaporation and FC (silica gel, hexane and hexane/ethyl acetate) gave the products **5** (for physical properties see table 6)

5e. $C_9H_{15}FO_2$ (174.22), ^1H NMR: 1.08 and 1.085 (each t, each 3H), 1 34 (t, 3H), 2.26 (dq, 7 5Hz, $^4J_{HF}$ = 3.3Hz, cis H_2C-C=C-F), 2 53 (dq, 7.5Hz, $^4J_{HF}$ = 1 7Hz, trans H_2C-C=C-F), 4.26 (q, 2H).

5f $C_{10}H_{15}FO_4$ (218.22). **Z-Isomer** (elutes first): IR 1725 (C=O), 1265 cm^{-1}, ^1H NMR. 1 11 (t, 3H), 1.34 and 1 36 (t, each 3H), 2 73 (qd, 7 5Hz, 1.8Hz, 2H, CF=C-CH_2), 4.28 and 4 31 (q, each 2H). **E-Isomer** IR. 1730 (C=O), 1670 (C=CF), 1320 cm^{-1}, ^1H NMR: 1.12 (t, 3H), 1 25 (t, 6H), 2 44 (qd, 8Hz, 3Hz, 2H, CF=C-CH_2), 4 28 (q, 4H);

Ethyl 2-fluoro-2(Z)-alkenoates **(10a-e)**, *general procedure* (see table 4) To a solution of sodium ethoxide (from 48 mg, 2mmol, sodium hydride and ethanol) and 10 mmol ethyl arylsulfinyl fluoroacetate (**2b-d**) in 10 ml ethanol was added over the period of one minute 12 mmol of the Michael acceptor (see table 4) and the temperature was allowed to reach 30-35°C After 2 hours 2 5 mmol acetic acid was added and the solvent removed in vacuo. The residue was dissolved in 50 ml toluene and refluxed for 15 minutes Evaporation and FC gave the products **10** (for physical properties see table 6)

Byproduct **11** (entry 5): ^1H NMR. 1.30 (t, 3H), 2.15 (s, 3H, =C-N-CO-CH_3), 4 2 (q, 2H), 5 80 (dd, 46Hz, 6Hz, CHF-C=), 6.44 (dd, 16.5Hz, 6Hz, CF-CH=), 7.53 (br, 1H, NH). IR: 3400, 1735, 1700 cm^{-1}.

Preparation of starting materials for **5b, m - p** *and* **s. 5b**. The reaction of 4.07 g (S)-(-)-2-methyl-1-butanol with 5.73 g methanesulfonyl chloride and 5.25 g triethylamine in 50 ml dichloromethane (3 h, rt) gave after workup and distillation 5 82g (76%) of *(S)-(+)-1-(2-methyl)-butyl methanesulfonate* {bp = 50-60°C/0.02 mbar, $[\alpha]_D^{20}$ =+3 6° (c = 3.2, chloroform)}. A mixture of 4 g of this sulfonate with 8 3 g lithium bromide and 35 ml acetone was refluxed for 2 hours. After evaporation the residue was dissolved in ether, washed with water and dried Evaporation and distillation gave 1 91g (52%) *(S)-(+)-1-bromo-2-methyl-butane* {bp = 120°C/760 mm, $[\alpha]_D^{20}$ = +3 6° (c = 3.8, chloroform)} **5m**: *2-Bromoethyl thexyldimethylsilyl ether* was obtained from 2-bromoethanol by a standard silylation procedure [44] **5n**: *3-Bromopropyl thexyldimethylsilyl ether* was obtained from 3-bromopropanol by a standard silylation procedure,[45] bp: 65-72°C/0.1 mbar. **5o**: The starting tosylate was prepared according to the literature.[46] Its reaction with LiBr in refluxing acetone gave after aqueous workup *(S)-3-bromo-2-methyl-1-propanol* {$[\alpha]_D^{20}$ =+5 3° (c = 1 3, chloroform)} which was protected as the ethoxyethoxy ether using ethylvinyl ether and pyridinium p-toluenesulfonate [42] to give *1-ethoxyethoxy-2-methyl-3-bromopropane.* **5p**: *3-Bromopropyl acetate* was obtained by acetylation of 3-bromo-1-propanol with acetylchloride in the presence of triethylamine in ether, bp = 72-77°C/28mbar. **5s**: *t-Butyl N-(2-bromoethyl)carbamate* was prepared according to Beylin and Goel.[47]

Table 6: Molecular weights and ^{1}H NMR data of ethyl 2-fluoro-2-alkenoates **5** and **10**[a] $CH_3CH_2OOC\text{-}CF\text{=}CH\text{-}C_{(4)}$

No	Formula	Mol weight[b]	CH=CF [ppm]	$J_{3,F}$ [Hz]	C-4-H [ppm][c]	C-5-H [ppm]	Additional ^{1}H-NMR signals[d] [ppm]
5a	$C_{10}H_{17}FO_2$	188 24	6 10 dt	34	2 23	1 45	0 9 (C-8-H), 1.27-1 37
5b	$C_9H_{15}FO_2$	174 22	5.91 dd	34	2 63	-	0 9-1 5 (11H)
5c	$C_{12}H_{13}FO_2$	208 23	6 28 dt	32	3.58	-	7 2-7 4 (5H)
5d	$C_8H_{11}FO_2$	158.17	6 58 dd	31	6 38	6 09	1 89 (d, C-6-H)
5g	$C_{13}H_{13}FO_4$	252 24	6 40 d	28	-	-	5 25 (PhCH), 7 4 (5H)
5h	$C_8H_{11}FO_4$	190 17	6.34 dt	31	3 32	-	3 73 (OCH_3)
5i	$C_{10}H_{15}FO_4$	218 22	6.13 dt	33	2 55	2 45	1 25, 4 14 (COOEt)
5k	$C_8H_{11}FO_4$	190 17	6 07 dd	31	5 79	-	3 9-4.2 (OCH_2CH_2O)
5l	$C_9H_{13}FO_4$	204 20	6 18 dt	33	2 63	4 98	3 8-4.05 (OCH_2CH_2O)
5m	$C_{14}H_{27}FO_3Si$	290 45	6 19 dt	32	4 38	-	$SiMe_2C_6H_{13}$ [e]
5n	$C_{15}H_{29}FO_3Si$	294 40	6 20 dt	34	2 44	3 66	$SiMe_2C_6H_{13}$ [e]
5o	$C_{12}H_{21}FO_4$	248 29	6 03 dd	34	3.08	3 3-3 8[f]	1 1-1.3 (12H), 4 67 (q, 1H, O-CH-O)
5p	$C_9H_{13}FO_4$	204 20	6.11 dt	33	2 57	4.13	2.05 (CH_3COO),
5q	$C_{14}H_{12}FNO_4$	277 25	6 15 dt	31	4 52	-	7 73, 7 86 (AA'BB')
5r	$C_{15}H_{14}FNO_4$	291 28	6 12 dt	31	2 66	3 80	7 72, 7 84 (AA'BB')
5s	$C_{11}H_{18}FNO_4$	247 27	6 14 dt	32 5	3 95	-	1 45 (s, 9H), 4 72 (NH)
10a	$C_9H_{13}FO_4$	204 20	6.33 dt	32	3 28	-	1 25 (3H), 4.17 (2H)· $COOC_2H_5$
10b	$C_7H_8FNO_2$	157 14	6 11 dt	30	3 31	-	-
10c	$C_{10}H_{15}FO_4$	218 22	6 25 dt	32 5	3 63	-	1 25-1.45 (9H), 4.17 (q, 2H, OCH_2)
10d	$C_9H_{13}FO_3$	188 20	6.38 dt	32.5	3.40	-	1 10 (t, 3H), 2.511 (q, 2H). COC_2H_5
10e	$C_{11}H_{16}FNO_6$	277 25	6 12 dd	31	5 37	-	1 2, 4 2, 2.05 (s, Ac), 6 28 (NH)

a) *other properties.* all compounds have IR absorptions at 1730 and 1680 cm^{-1} due to the C=O and C=CF absorption respectively, **5b**· bp 90°C/20mbar, $[\alpha]_D^{20}$=+24.6° (c=1.3, $CHCl_3$); **5n**. bp. 95-98°C/0.04mbar, **5s** IR 3440 (NH), 1710 (O=CON), **10c** IR 2250 (CN), b) molecular weights are confirmed by mass spectroscopy. c) protons at C-4 exhibit a long range coupling with the fluorine at C-2 with a coupling constant of about 2 Hz, d) all compounds have signals due to the $COOCH_2CH_3$ group: 1.33 (t, 3H), 4 28 (q, 2H); e) ^{1}H-NMR-signals of the $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$ group. 0.1 (s, 6H, $Si(CH_3)_2$), 0.81 (s, 6H, Si-$C(CH_3)_2$), 0.87 (d, 6H, Si-C-$C(CH_3)_2$, 1 6 (m, 1H, Si-C-C-H), f) C-5-H together with CH_2-O signal in ethoxyethoxy protecting group

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