Pergamon

Tetrahedron 54 (1998) 10801–10810

TETRAHEDRON

Synthesis of α-Fluoro-β-Hydroxy Alkylsulfanyl Esters *via* a Nucleophilic Fluorination of Sulfides

C. Jouen, S. Lemaître, T. Lequeux* , J.C. Pommelet

Laboratoire de Chimie Moléculaire et Thio-organique, UMR-CNRS 6507
Université de Caen - ISMRA , 6 Bd du Maréchal Juin - F 14050 Caen

Received 5 May 1998; accepted 1 July 1998

Abstract : By halogen-exchange reaction using NEt_3-3HF as fluoride source, methyl 2-fluoro-2-alkylsulfanyl acetate **3a-d** could be obtained in good yields. Their ester enolates reacted with aromatic or aliphatic aldehydes, to lead to methyl α-alkylsulfanyl-α-fluoro-β-hydroxy esters **4-8**. By using benzaldehyde as electrophile, the *retro*-aldol reaction could be favorised by a temperature effect. The selective formation of the *syn* or the *anti* diastereoisomers has been controled.

The introduction of fluorine atoms into biological active compounds strongly modifie their properties. Substitution of a hydrogen atom or hydroxyl group by a fluorine atom has been largely practised.[1-3] Other interests in bioorganic and medicinal chemistry are the introduction of a fluoroalkene moiety into peptide isosteres or ribonucleosides for the design of enzyme inhibitors.[4-9] In this goal, fluoro-sulfur chemistry seems to be attractive in order to generate a fluoroalkene motif in various substrats. Alkylsulfanyl acetates **1** were efficient building-block to prepare α-alkylsulfanyl-β-hydroxy esters derivatives.[10-14] These later were generaly used to study the sulfur elimination reactions to introduce a double bond,[15-17] or to generate an episulfonium ion to introduce a nucleophile.[18,19] The most widespread methods for the synthesis of alkylsulfanyl-fluoroesters need to handle expensive bromofluoroesters as starting materials.[20,21] Fuchigami[22] and Laurent[23] too reported their preparation, by direct fluorination using anodic oxidation of sulfides in the presence of a large excess of triethylamine trihydrogenofluoride (NEt_3-3HF). On the other hand, McCarthy showed that fluorosulfides could be formed from sulfoxides, through a Pummerer-like rearrangement induced by the diethylaminosulfur trifluoride (DAST) .[24] In this connexion, we have explored a cheapest and general alternative approach for the preparation of alkylsulfanyl-fluoroesters from fluor-free starting materials. In this paper we reported our full results concerning their synthesis and the reactivity of their ester enolates towards carbonyl electrophiles.

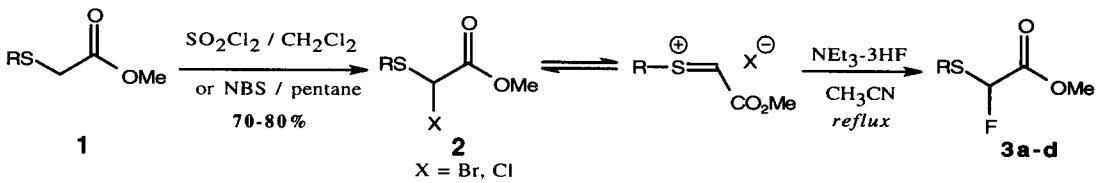
* Thierry.Lequeux@ismra.fr ; fax : (33) 02 31 45 28 77

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00639-5

Results and Discussion

Recently, we reported a general preparation of α-chloro-α-fluoro-alkylsulfanyl acetates by a nucleophilic halogen exchange reaction. In these cases, the dichloromethylene center was highly reactive towards nucleophiles and the selective exchange of one chlorine by a fluorine atom was successfull.[25,26]

In the same approach, we have investigated the possible chlorine-fluorine atoms exchange from monochloro-alkylsulfanyl acetates **2**. The synthesis of alkyl or arylsulfanyl-acetates and their chlorination or bromination are well documented.[27] Halogenations can be performed using sulfuryl chloride (1eq.), N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS), to lead to chloro- or bromoalkylsulfanyl esters **2** in good yields. The displacement of the halogen atom from α-chloro or bromo-alkylsulfanyl-esters was attempted with various fluoride sources. Attempts with KF failed. However, with the dihydrogentrifluoride polymer-supported[28] $P^+H_2F_3^-$ formation of products was detected after a long reaction time (24h), but in a relatively moderate yields (30-35%). Several attempts, under different experimental conditions, showed that the halogen exchange reaction could be effective with the more reactive reagent NEt_3-3HF complex. By refluxing an acetonitrile solution of a mixture of this complex and chloro-alkylsulfanyl esters **2**, fluorinated products **3a-d** could be obtained in good yields (Scheme 1 ; Table I).



Scheme 1

Table I : *Preparation of monofluoroesters 3*

Entry	X	R	*Reagent (eq.)*	*Additive*	*Time*	*prod. : yield*[a]
1	Cl	C_2H_5-	NEt_3-3HF (4 *eq.*)	*none*	2h	**3a** : 75
2	Br	C_2H_5-	NEt_3-3HF (4 *eq.*)	*none*	1.5h	**3a** : 69
3	Cl	$(CH_3)_2CH$-	NEt_3-3HF (4 *eq.*)	*none*	2h	**3b** : 76
4	Cl	$C_6H_5CH_2$-	NEt_3-3HF (4 *eq.*)	*none*	7h	**3c** : 62
5	Cl	C_6H_5-	NEt_3-3HF (6 *eq.*)	*none*	70h	**3d** (65)[b]
6	Cl	C_6H_5-	NEt_3-3HF (6 *eq.*)	$ZnBr_2$	18h	**3d** : 66

a. isolated yield ; b. conversion determinated by ^1H NMR.

The reaction required not less than four fold excess of reagents, in order to limit the formation of by-products after a long reaction time.

The influence of the halogen nature was not so expected (*Entry* 2). The bromo-alkylsulfanyl ester reacted slightly rather than the chlorinated analogue, but the yield was limited by its thermal unstability.

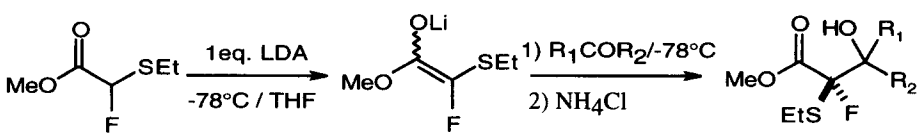
In contrast, the rate of the halogen-exchange step strongly depends on the alkylsulfanyl moiety, decreasing

from ethyl-, to benzyl- and phenylsulfanyl substituents (*Entry* 1, 4, 5). The inductive effect of these substituents seems to be responsible of these differences of reactivity. These suggest a two steps mecanism involving the formation of sulfenium intermediate (Scheme 1). The electronic character of the alkylsulfanyl moiety appeared to be the driving-force of this first step. The partial delocalisation of the lone pairs of the sulfur atom contributed to the formation of the sulfenium intermediate, only when sulfur atom was substituted by an electron-donating group (ethyl, benzyl). If it was not confirmed, the complete conversion failed, even after a long reaction time (*Entry* 5). Attempt to favorise the formation of the sulfenium and catalyse this atoms exchange reaction by addition of mild Lewis acid, was sucessfull.[29] In presence of zinc bromide (1 eq.), the displacement of the chlorine atom was complete in a raisonnable reaction time. Methyl 2-fluoro-2-phenylsulfanyl acetate was obtained in 68% isolated yield after 18h (*Entry* 6).

This new procedure appeared to be more efficient than other methodologies,[20-24] and allowed a simple and cheapest route to a large variety of α-fluoro-alkylsulfanyl esters in good yields. By contrast with others, this method allowed to save steps of formation of intermediate sulfoxide and avoid to handle expensive reagents diethylaminosulfur trifluoride reagent (DAST) and ethyl bromofluoroacetate.

In order to prepare β-hydroxy-α-alkylsulfanyl esters derivatives **4-8** as potential precursor of fluoroalkenes, we studied the reactivity of the ester enolates, generated from α-fluoro-alkylsulfanyl esters **3**, towards carbonyl compounds. The addition of non fluorinated ester enolates to aldehydes and ketones are well documented.[30,10-14] Diastereoselective additions have been reported using titanium enolate, which favored the formation of the *syn* diastereoisomer.[12] Some examples described the reactivity of sulfoxides,[20] but only a short communication from B. Ducep *et al.* described the condensation of corresponding sulfides, such as ethyl fluoro-phenylsulfanyl acetate,[21] and aldehydes. Aldol products were used as precursors of fluoroalkenes by sulfur elimination,[31,32] or α,α-difluoroesters *via* the formation of episulfonium. [21] These, prompt us to report our full results concerning the reactivity and the selectivity of the addition reaction of the α-fluoro-alkylsulfanyl-acetates towards carbonyl electrophiles.

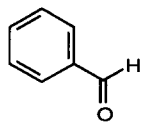
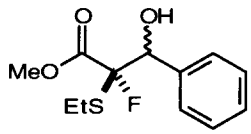
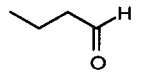
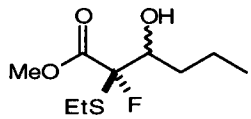
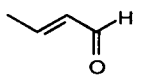
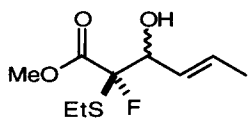
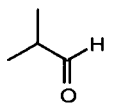
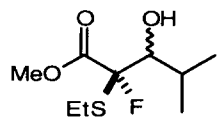
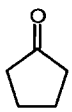
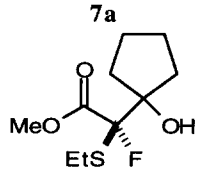
The lithiated anions derived from ester **3a** have been generated with LDA at -78°C, and allowed to react with aromatic or aliphatic aldehydes and ketone, leading to a diastereoisomeric mixture of methyl 2-fluoro-2-ethylsulfanyl-3-hydroxy-3-alkyl-alkanoate **4a-8a** (Scheme 2). Results are summarised in Table II.



3a **4a-8a**

Scheme 2

Table II : *Synthesis of α-alkylsulfanyl-α-fluoro-β-hydroxyesters*

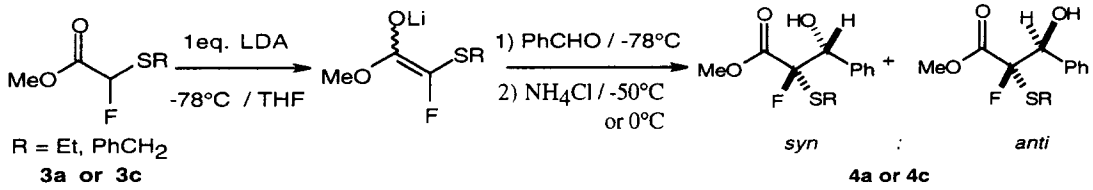
Electrophile	Product[a]	Yield (%)[b, c]
	 **4a**	56
	 **5a**	52
	 **6a**	53
	 **7a**	54
	 **8a**	52

a. All reactions were performed at -78°C during 2.5h b. isolated yield. c mixture of diastereoisomers (1:1 ratio)

The reaction afforded adducts in moderate yields with aldehydes, and cyclopentanone. The crude products was always contaminated by an important quantity of electrophile, but without traces of starting sulfanyl ester. The total deprotonation of the sulfanyl ester has been checked by quenching the anion with D_2O. The anion was formed by addition of neat sulfide on a LDA solution in THF, and after 1 hour of stirring in presence of D_2O, the mixture was allowed to warmed to 0°C. The crude deuterated ester formed was caracterised by fluorine NMR, and presented only a triplet ($^2J_{FD}$ = 14 Hz) at -163.5 ppm without other products. The addition of TMEDA, zinc bromide, or a simultaneous addition of the thioether and the electrophile to a solution of LDA, did not increase significantly the yields. These results showed a thermal instability of the ester enolates at -78°C. A complete conversion of the electrophile was observed only with no less than 3 equivalents of anion. This suggested a slight decomposition of the anion during the process.

By comparison with the recent observations reported by Ducep et *al.*,[21] which reported a better yield from phenylsulfanyl acetate (80%), the nature of the sulfanyl group seems to be important. The thermal stability of the ester enolate was strongly depending on the electron-withdrawing character of alkylsulfanyl moiety. Attempts to quench the ester enolates by addition of chlorotrimethylsilane lead to a unstable mixture of fluorinated products.

In each cases, the aldolisation reaction lead to products with a poor control of the selectivity. At -78°C, a separable diastereoisomeric mixture in 1:1 ratio was obtained. However, using benzaldehyde as electrophile the esters **3a** or **3c**, yielded stereoselectively to one of the diastereoisomers **4a** or **4c** (scheme 3). The stereoselectivity of this reaction was strongly depending on the temperature of hydrolysis. The aldehyde was added at -78°C in few minutes, and the mixture was gradually warmed to 0°C during 2.5h, before to be hydrolysed by addition of aqueous NH_4Cl. The ^{19}F and ^1H NMR analysis of the crude mixture showed the *anti* isomer as the major product. By contrast, opposite results were observed at -50°C. After warmed up at -50°C and hydrolysis, the *syn* isomer were preferentially obtained (Table III).



Scheme 3

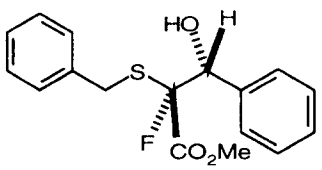
Table III : *Diastereoselective formation of fluoroesters*

Ester	Temp.[a]	Product	syn : anti[b]	yield
3a	-78°C	4a	60 : 40	56
	-50°C		72 : 28	49
	0°C		14 : 86	52
3c	-78°C	4c	56 : 44	52
	-50°C		68 : 32	51
	0°C		20 : 80	49

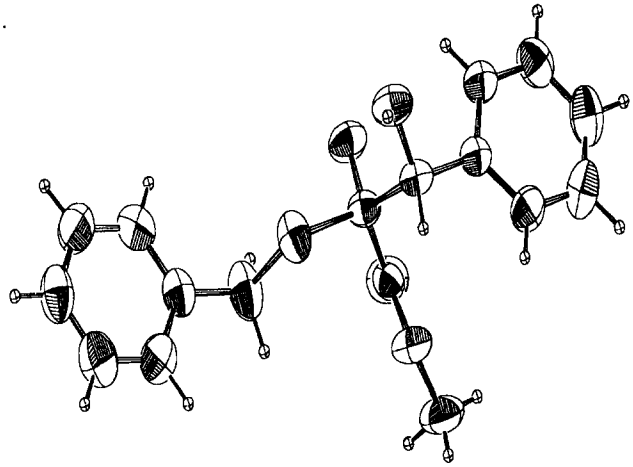
a. Temperature of hydrolysis. b. Crude ratio determinated by ^{19}F and ^1H NMR.

Attempted to control the selectivity by addition of strong Lewis acid ($TiCl_4$) resulted in the decomposition of products in the medium.

Isolation and recristallisation of the *syn* **4c** isomer allowed its structure determination by X-*Ray* [33] analysis (Scheme 4). By correlation with the fluorine and proton NMR data, the *syn* and *anti* NMR shifts of the adducts **4c** and **4a**, were unambiguously located .

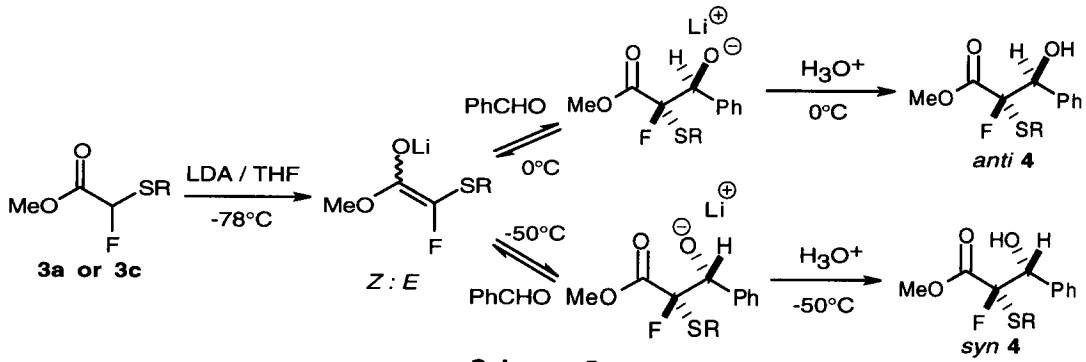


syn **4c**



Scheme 4 : ORTEP diagram of **4c**

This selectivity was depending on the alcoholates stability in the medium. Pure alcoholates were formed by stirring isolated *syn* adduct **4a** in presence of LDA at -78°C, and the mixture was slowly warm-up to 0°C during 2h (Scheme 5). The resulting pure *syn* **4a** was converted in a mixture of *syn* , *anti* isomers **4a**, benzaldehyde (2.5 / 4 / 3.5 ratio) contaminated with some traces of **3a**. Performing the reaction of **3a** with the benzaldehyde in presence of freshly dried zinc bromide (1 eq.), the 1:1 *syn* : *anti* ratio was maintained between -78° and 0°C. These suggest that a *retro*-aldol reaction proceed between -78°C and 0°C, and did not occur in presence of zinc bromide. The addition of zinc bromide in the medium should stabilised the intermediate alcoholates. This selectivity was limited and not observed with aliphatic aldehydes. The addition of ester enolates of **3a** with butanal, or crotonaldehyde provided a diastereoisomeric mixture of products **5a** or **6a** in about 1:1 ratio at different temperatures.



Scheme 5

In conclusion, we reported an efficient synthesis of 2-alkylsulfanyl-2-fluoro esters by halogen-exchange reaction using NEt_3-3HF as a fluoride source. Ester enolates generated from these esters could added to carbonyl compounds including cyclic ketone, to afford a separable diastereoisomeric mixture of α-alkylsulfanyl-α-fluoro-β-hydroxy esters. These reactions opened a general route to highly functionnalised fluoroesters in only 3 steps from easily available starting materials. The selectivity of the addition of these ester enolates could be controled only with benzaldehyde. This selectivity is a result of a *retro*-aldol reaction, allowing an access to the *anti* isomers, which cannot be prepared in presence of Lewis acid. Extension of the selective formation of β-hydroxy-α-alkylsulfanyl esters to other aromatic aldehydes, and reactivity of fluoro-alkylsulfanyl ester enolates towards other electrophiles are under investigations.

Acknowledgements : Authors gratfully thanks Dr J-P. Bégué (CNRS) for his critics during the preparation of this manuscript. We wish to thank Mr S. Leroux for his contribution during the preparation of starting sulfides.

Experimentals

^1H NMR were recorded at 250 MHz and ^{13}C NMR at 62 MHz on a *Brucker AC-250 MHz* ^{19}F NMR were recorded at 75.3 MHz on a *Brucker WP-80 MHz* spectrometers, using TMS or $CFCl_3$ as reference. Mass spectra were performed on a *Nermag Riber R10.* All solvents were purified by standard methods. Sulfides were prepared by the usual procedure.[25]

Methyl 2-ethylsulfanyl-2-fluoroacetate 3a

To a solution of methyl 2-chloro-2-ethylsulfanylacetate (2.4 g, 14 mmol) in MeCN (20mL) was added dropwise $Et_3N.3HF$ (9.4 mL, 58 mmol). This solution was refluxed under nitrogen during 2 hours. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous solution of sodium bicarbonate. The organic layers were washed twice with brine, dried and concentrated. The residue was distilled under reduced pressure (bp 25°C/0.03 Torr) to lead to 1.6 g (75%) of **3a**.

^1H NMR ($CDCl_3$) : δ = 1.33 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3CH_2S) ; 2.77 (m, 2H, CH_3CH_2S) ; 3.85 (s, 3H, OCH_3) ; 5.95 (d, $^1J_{HF}$ = 52.0 Hz, 1H, *C*HFCO). ^{13}C NMR ($CDCl_3$) : δ = 15.0 (CH_3CH_2) ; 24.8 (CH_3CH_2) ; 53.0 (OCH_3) ; 92.2 (d, $^1J_{CF}$ = 228.8 Hz, *C*HFCO) ; 166.8 (d, $^2J_{CF}$ = 30.3 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -162.7 (d, $^2J_{HF}$ = 52.0 Hz, 1F, CH*F*). Anal.Calcd. for $C_5H_9O_2SF$ (152.18) : C, 39.46 ; H, 5.96. Found C, 38.79 ; H, 5.84.

Following the above procedure from methyl 2-bromo-2-ethylsulfanylacetate (1.06g, 4.98 mmol) and $Et_3N.3HF$ (3.2 mL, 19.8 mmol) 520 mg (69%) of **3a** was obtained after 1.5h of reflux under nitrogen.

Methyl 2-isopropylsulfanyl-2-fluoroacetate 3b

Following the above procedure from methyl 2-chloro-2-isopropylsulfanylacetate (0.8 g, 4.42 mmol) and $Et_3N.3HF$ (2.87 mL, 17.7 mmol), 0.75 g of crude **3b** was obtained. After usual work-up, the residue was distilled under reduced pressure (bp 30°C/0.04 Torr) to lead to. 0.561g (76%) of **3b.**

^1H NMR ($CDCl_3$) : δ = 1.26 (d, $^3J_{HH}$ = 6.8 Hz, 3H, $(CH_3)_2CHS$) ; 1.32 (d, $^3J_{HH}$ = 6.7 Hz, 3H, $(CH_3)_2CHS$) ; 3.19 (dsept, $^3J_{HH}$ = 6.7 Hz, $^4J_{HF}$ = 1.8, Hz, 1H, $(CH_3)_2CHS$) ; 3.77 (s, 3H, OCH_3) ; 5.95 (d, $^2J_{HF}$ = 54.0 Hz, 1H, *C*HFCO). ^{13}C NMR ($CDCl_3$) : δ = 23.6 ($(CH_3)_2CH$) ; 24.1 ($(CH_3)_2CH$) ; 36.4 ($(CH_3)_2CH$) ; 52.9 (OCH_3) ; 92.3 (d, $^1J_{CF}$ = 228.1 Hz, *C*HFCO) ; 166.8 ((d, $^2J_{CF}$ = 29.1 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -160.0 (d, $^2J_{HF}$ = 53.7 Hz, 1F, CH*F*). Anal.Calcd. for $C_6H_{11}O_2SF$ (166.22) : C, 43.36 ; H, 6.67. Found C, 42.97 ; H, 6.62.

Methyl 2-benzylsulfanyl-2-fluoroacetate 3c

To a solution of methyl 2-benzylsulfanyl-2-chloroacetate (0.94 g, 4.07 mmol) in MeCN was added dropwise NEt_3-3HF (2.65 mL, 16.3 mmol). This refluxed under nitrogen for 7h. After usual work-up, the residue was distilled under reduced pressure (bp 110°C/0.02 Torr) to lead to 540 mg (62%) of **3c**.

^1H NMR ($CDCl_3$) : δ = 3.72 (s, 3H, OCH_3) ; 3.94 et 3.99 (ABX syst., $^2J_{H4AH4B}$ = 12.1 Hz et $^4J_{H4F}$ = 2 Hz, 2H, $PhCH_2$) ; 5.83 (d, $^1J_{HF}$ = 52.3 Hz, 1H, *C*HF) ; 7.33 (m, 5*H*). ^{13}C NMR ($CDCl_3$) : δ = 34.2 (CH_2Ph) ; 53 (CH_3O) ; 91.1 (d, $^1J_{CF}$ = 225 Hz, *C*HF) ; 127.8, 128.9, 129.3, 135.6 (aromatic*C*) ; 166.9 (*C*O). ^{19}F NMR ($CDCl_3$) : δ = -165.3 (d, $^1J_{HF}$ = 52.3 Hz). Anal.Calc. for $C_{10}H_{11}O_2SF$ (214.26) : C, 56.06 ; H, 5.17, . Found C, 55.46 ; H, 4.97.

Methyl 2-phenylsulfanyl-2-fluoroacetate 3d

To a suspension of freshly dried zinc bromide (0.63 g, 2.8 mmol), was added a solution of methyl 2-chloro-2-phenylsulfanylacetate (0.6 g, 2.8 mmol) in MeCN and neat NEt_3-3HF (2.72 mL, 16.8 mmol). After 18h of reflux, the cooled solution was washed, and the residue was distilled under reduced pressure (bp 70°C/0.03 Torr) to lead to 0.37 g (66%) of **3d**.

^1H NMR ($CDCl_3$) : δ = 3.70 (s, 3H, CH_3O) ; 6.1 (d, $^2J_{HF}$ = 52.4 Hz, 1H, *C*HF) ; 7.37 (m, 3*H*) ; 7.53 (m, 2*H*). ^{13}C NMR ($CDCl_3$) : δ = 52.9 (CH_3O) ; 94.5 (d, $^1J_{CF}$ = 233 Hz, *C*HF) ; 129.2, 129.4, 129.7, 134.2 (aromatic *C*) ; 165.7 (d, $^2J_{CF}$ = 29 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -158.8 (d, $^2J_{HF}$ = 52.4 Hz). Anal. Calc. for $C_9H_9O_2SF$ (200.23) ; C, 53.99 ; H, 4.53 . Found C, 54.06 ; H, 4.55 .

Condensation of fluoro sulfides with carbonylated electrophiles : General procedure

To a solution of diisopropylamine (12 mmol) in THF (4 mL) under nitrogen was added dropwise butyllithium (10.6 mL, 1.2 M in hexane, 11.5 mmol) at -78°C. After 20 min of stirring at -20°C, the solution was cooled (-78°C) and neat fluorosulfide (10 mmol) was added. After 30 min of stirring at -78°C, the electrophile was added (10.2 mmol) and the reaction mixture was stirred over 2.5h. The mixture was hydrolyzed by addition of aqueous solution of ammonium chloride at -78°C. The solution was extracted with CH_2Cl_2 at room temperature, and the combined organic layers was dried ($MgSO_4$), and concentrated. The oily residue was purified by flash chromatography (EtOAc/cyclohexane, 1:6).

When the hydrolysis was done at -50°C or 0°C, the electrophile was added at -78°C, and the resulting mixture was slowly warmed to -50°C or 0°C during 2.5h before hydrolysis. After usual work-up, adducts were isolated by FC.

Methyl 2-ethylsulfanyl-2-fluoro-3-hydroxy-3-phenyl-propanoate 4a

At -78°C, from methyl 2-fluoro-2-ethylsulfanylacetate **3a** (173 mg, 1.14 mmol) and benzaldehyde (0.12 mL, 1.16 mmol), a diastereomeric mixture of **4a** was obtained in a 6/4 *syn/anti* ratio (^{19}F and ^{1}H NMR). After chromatography, 59 mg of *syn* isomer **4a** (20%), 75 mg of a diastereomeric mixture (26%) and 30 mg of *anti* isomer **4a** (10%) were obtained.

At -50°C, from **3a** (200 mg, 1.31 mmol) and benzaldehyde (0.14 mL, 1.34 mmol), a diastereomeric mixture of **4a** was obtained in a 72/28 *syn/anti* ratio (^{19}F and ^{1}H NMR). After chromatography, 165mg of diastereomeric mixture **4a** (49%) was obtained.

At 0°C, from **3a** (200 mg, 1.31 mmol) and benzaldehyde (0.14 mL, 1.34 mmol), a diastereomeric mixture of **4a** was obtained in a 14/86 *syn/anti* ratio (^{19}F and ^{1}H NMR). After chromatography, 175 mg of a diastereomeric mixture **4a** (52%) was obtained.

syn isomer : ^{1}H NMR ($CDCl_3$) : δ = 1.19 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H, CH_3CH_2S) ; 2.62 (m, 2H, CH_3CH_2S) ; 2.94 (m, 1H, CHO*H*) ; 3.64 (s, 3H, OCH_3) ; 5.07 (d, $^{3}J_{HF}$ = 17.7 Hz, 1H, *C*HCF) ; 7.3 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (CH_3CH_2) ; 23.9 (CH_3CH_2) ; 52.9 (OCH_3) ; 76.5 (d, $^{2}J_{CF}$ = 20.6 Hz, 1C, *C*HCF) ; 103.6 (d, $^{1}J_{CF}$ = 240.6 Hz, *C*FCH) ; 127.9, 128.3, 129.0, 136.8 (Phenyl) ; 167.8 (d, $^{2}J_{CF}$ = 30.5 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -152.1 (d, $^{3}J_{HF}$ = 17.6 Hz, 1F, CHC*F*).

anti isomer : ^{1}H NMR ($CDCl_3$) : δ = 1.13 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3CH_2S) ; 2.52 (m, 2H, CH_3CH_2S) ; 2.83 (m, 1H, CHO*H*) ; 3.82 (s, 3H, OCH_3) ; 5.08 (d, $^{3}J_{HF}$ = 18.6 Hz, 1H, *C*HCF) ; 7.3 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) : δ = 14.4 (CH_3CH_2) ; 24.1 (CH_3CH_2) ; 53.3 (OCH_3) ; 76.9 (d, $^{2}J_{CF}$ = 20.6 Hz, 1C, *C*HCF) ; 104.8 (d, $^{1}J_{CF}$ = 241.5 Hz, *C*FCH) ; 128.1, 128.4, 129.2, 136.9 (Phenyl) ; 168.1 (d, $^{2}J_{CF}$ = 32.3 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -154.9 (d, $^{3}J_{HF}$ = 18.3 Hz, 1F, CHC*F*). MS : m/z (%) = 258 ([M]$^{+\cdot}$, 1.3) ; 177 (11) ; 152 (100) ; 60 (66) ; 51 (11). Anal.Calc. for $C_{12}H_{15}O_3SF$ (258.31) : C, 55.80 ; H, 5.85. Found C, 55.32 ; H, 5.61.

Methyl 2-ethylsulfanyl-2-fluoro-3-hydroxy-hexanoate 5a

At -78°C, from methyl 2-fluoro-2-ethylsulfanylacetate **3a** (201 mg, 1.31 mmol) and butanal (0.12 mL, 1.34 mmol), a diastereomeric mixture of **3a** was obtained in a 55/45 *syn/anti* ratio (^{19}F and ^{1}H NMR in the crude product). By column chromatography 155 mg (52%) of diastereomers was obtained .

syn isomer : ^{1}H NMR ($CDCl_3$) : δ = 0.87 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H, $CH_3CH_2CH_2CHOH$) ; 1.20 (t, $^{3}J_{HH}$ = 7.6 Hz, 3H, CH_3CH_2S) ; 1.2-1.7 (m, 4H, $CH_3CH_2CH_2CHOH$) ; 2.46 (m, 1H, CHO*H*) ; 2.4 to 2.8 (m, 2H, CH_3CH_2S) ; 3.79 (s, 3H, OCH_3) ; 3.97 (ddd, $^{3}J_{H3F}$ = 16.4 Hz, $^{3}J_{H3H4}$ = 10.0 Hz, $^{3}J_{H3H4}$ = 2.2 Hz, 1H, *C*HCF). ^{13}C NMR ($CDCl_3$) : δ = 13.7 ($CH_3CH_2CH_2CHOH$) ; 14.6 (CH_3CH_2) ; 19.1 ($CH_3CH_2CH_2CHOH$) ; 23.4 (CH_3CH_2) ; 33.7 ($CH_3CH_2CH_2CHOH$) ; 53.0 (OCH_3) ; 74.5 (d, $^{2}J_{CF}$ = 22.4 Hz, 1C, *C*HCF) ; 105.4 (d, $^{1}J_{CF}$ = 235.2 Hz, 1C, CH*C*F) ; 168.2 (d, $^{2}J_{CF}$ = 32.3 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -149.8 (d, $^{3}J_{HF}$ = 16.2 Hz, 1F, CHC*F*).

anti isomer : ^{1}H NMR ($CDCl_3$) : δ = 0.89 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H, $CH_3CH_2CH_2CHOH$) ; 1.20 (t, $^{3}J_{HH}$ = 7.6 Hz, 3H, CH_3CH_2S) ; 1.2-1.8 (m, 4H, $CH_3CH_2CH_2CHOH$) ; 2.10 (m, 1H, CHO*H*) ; 2.4 to 2.8 (m, 2H, CH_3CH_2S) ; 3.80 (s, 3H, OCH_3) ; 3.97 (ddd, $^{3}J_{H3F}$ = 17.7 Hz, $^{3}J_{H3H4}$ = 10.0 Hz, $^{3}J_{H3H4}$ = 2.0 Hz, 1H, *C*HCF). ^{13}C NMR ($CDCl_3$) : δ = 13.7 ($CH_3CH_2CH_2CHOH$) ; 14.6 (CH_3CH_2) ; 18.9 ($CH_3CH_2CH_2CHOH$) ; 23.9 (CH_3CH_2) ; 33.3 ($CH_3CH_2CH_2CHOH$) ; 53.0 (OCH_3) ; 74.4 (d, $^{2}J_{CF}$ = 23.3 Hz, 1C, *C*HCF) ; 105.4 (d, $^{1}J_{CF}$ = 234.3 Hz, 1C, CH*C*F) ; 168.3 (d, $^{2}J_{CF}$ = 33.2 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -154.9 (d, $^{3}J_{HF}$ = 18 Hz, 1F, CHC*F*). MS : m/z (%) = 224 ([M]$^{+\cdot}$, 0.7) ; 164 (3.3) ; 152 (81) ; 151 (57) ; 120 (100) ; 73 (10) ; 59 (34). Anal.Calc. for $C_9H_{17}O_3SF$ (224.29) : C, 48.19 ; H, 7.64. Found C, 48.89 ; H, 7.81.

Methyl (*E*)-2-ethylsulfanyl-2-fluoro-3-hydroxy-hexen-4-oate 6a

At -78°C, from **3a** (199 mg, 1.31 mmol) and (*E*) crotonaldehyde (0.11 mL, 1.34 mmol), a diastereomeric mixture of **6a** was obtained in a 60/40 *syn/anti* ratio (^{19}F and ^{1}H NMR). After purification 154 mg (53%) of diastereomers were obtained.

syn isomer : ^{1}H NMR ($CDCl_3$) : δ = 1.20 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H, CH_3CH_2S) ; 1.66 (dd, $^{4}J_{H4H6}$ = 1.2 Hz, $^{3}J_{H5H6}$ = 6.5 Hz, 3H, CH_3CH=CH) ; 2.4 (m, 1H, CHO*H*) ; 2.61 (m, 2H, CH_3CH_2S) ; 3.77 (s, 3H, OCH_3) ; 4.42 (dd, $^{3}J_{H3F}$ = 16.6 Hz, $^{3}J_{H3H4}$ = 7.6 Hz, 1H, *C*HCF) ; 5.53 (ddq, $^{4}J_{H4H6}$ = 1.2 Hz, $^{3}J_{H3H4}$ = 7.6 Hz, $^{3}J_{H4H5}$ = 15.6 Hz, 1H, CH_3CH=C*H*) ; 5.78 (dq, $^{3}J_{H5H6}$ = 6.4 Hz, $^{3}J_{H4H5}$ = 15.6 Hz, 1H, CH_3CH=CH). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (CH_3CH_2) ; 17.9 (CH_3CH=CH) ; 23.6 (CH_3CH_2) ; 53.0 (OCH_3) ; 76.3 (d,

$^2J_{CF}$ = 22.4 Hz, 1C, *C*HCF) ; 104.8 (d, $^1J_{CF}$ = 235.2 Hz, 1C, CH*C*F) ; 126.2 (d, $^3J_{CF}$ = 3.6 Hz, CH_3CH=*C*H) ; 132.4 (CH_3*C*H=CH) ; 167.8 (d, $^2J_{CF}$ = 31.4 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -149.5 (d, $^3J_{HF}$ = 16.5 Hz, 1F, CHC*F*).

anti isomer : ^{1}H NMR ($CDCl_3$) : δ = 1.18 (t, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_3$CH$_2$S) ; 1.70 (dd, $^4J_{H4H6}$ = 1.5 Hz, $^3J_{H5H6}$ = 6.4 Hz, 3H, C*H*$_3$CH=CH) ; 2.6 (m, 1H, CHO*H*) ; 2.4-2.8 (m, 2H, CH_3CH_2S) ; 3.80 (s, 3H, OC*H*$_3$) ; 4.45 (dd, $^3J_{H3F}$ = 18.2 Hz, $^3J_{H3H4}$ = 4.3 Hz, 1H, C*H*CF) ; 5.52 (dd, $^3J_{H3H4}$ = 7.6 Hz, $^3J_{H4H5}$ = 15.3 Hz, 1H, CH_3CH=C*H*) ; 5.82 (dq, $^3J_{H5H6}$ = 6.4 Hz, $^3J_{H4H5}$ = 15.6 Hz, 1H, CH_3CH=CH). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (*C*H$_3$CH$_2$) ; 17.9 (*C*H$_3$CH=CH) ; 23.6 (CH_3CH_2) ; 53.1 (O*C*H$_3$) ; 75.8 (d, $^2J_{CF}$ = 21.5 Hz, 1C, *C*HCF) ; 104.8 (d, $^1J_{CF}$ = 236.1 Hz, 1C, CH*C*F) ; 125.8 (d, $^3J_{CF}$ = 1.8 Hz, CH_3CH=*C*H) ; 132.8 (CH_3*C*H=CH) ; 168.1 (d, $^2J_{CF}$ = 32.3 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -155.0 (d, $^3J_{HF}$ = 18.2 Hz, 1F, CHC*F*). MS : m/z (%) = 222 ([M]$^{+\cdot}$, 0.9) ; 162 (3.7) ; 152 (100) ; 151 (77) ; 120 (83) ; 71 (52) ; 59 (30). Anal.Calc. for $C_9H_{15}O_3SF$ (222.27) : C, 48.63 ; H, 6.80. Found C, 48.49 ; H, 6.97.

Methyl 2-ethylsulfanyl-2-fluoro-3-hydroxy-4-methyl-pentanoate 7a

At -78°C, from **3a** (200 mg, 1.31 mmol) and isobutyraldehyde (0.12 mL, 1.34 mmol), a diastereomeric mixture of **7a** was obtained in a 50/50 *syn/anti* ratio (^{1}H NMR). Purification lead to 158 mg (54%) of a diastereomeric mixture .

syn isomer : ^{1}H NMR ($CDCl_3$) : δ = 0.92 (d, $^3J_{HH}$ = 6.7 Hz, 3H, (C*H*$_3$)$_2$CH) ; 0.94 (dd, $^4J_{HF}$ = 1.5 Hz, $^3J_{HH}$ = 6.7 Hz, 3H, (C*H*$_3$)$_2$CH) ; 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_3$CH$_2$S) ; 1.82 (sept, $^3J_{HH}$ = 4.6 Hz, 1H, (CH$_3$)$_2$C*H*) ; 2.18 (d, $^3J_{H3H3'}$ = 8.2 Hz, 1H, CHO*H*) ; 2.58 (m, 2H, CH_3CH_2S) ; 3.79 (s, 3H, OC*H*$_3$) ; 3.92 (ddd, $^3J_{H3H3'}$ = 8.2 Hz, $^3J_{H3H4}$ = 4.6 Hz, $^3J_{H3F}$ = 21.2 Hz, 1H, C*H*CF). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (*C*H$_3$CH$_2$) ; 17.2 and 20.6 ((*C*H$_3$)$_2$CH) ; 23.5 (CH_3CH_2) ; 31.2 (CH_3)$_2$*C*H) ; 53.1 (O*C*H$_3$) ; 78.2 (d, $^2J_{CF}$ = 20.6 Hz, 1C, *C*HCF) ; 106.0 (d, $^1J_{CF}$ = 238.8 Hz, 1C, CH*C*F) ; 168.4 (d, $^2J_{CF}$ = 31.4 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -152.8 (d, $^3J_{HF}$ = 21.2 Hz, 1F, CHC*F*).

anti isomer : ^{1}H NMR ($CDCl_3$) : δ = 0.91 (dd, $^3J_{HH}$ = 6.7 Hz, $^4J_{HF}$= 2.1 Hz, 3H, (C*H*$_3$)$_2$CH)) ; 0.99 (d, $^3J_{HH}$ = 7.0 Hz, 3H, (C*H*$_3$)$_2$CH)) ; 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_3$CH$_2$S) ; 2.13 (dsept, $^3J_{H3H4}$ = 2.5 Hz, $^3J_{HH}$ = 10.1 Hz, 1H, (CH$_3$)$_2$C*H*)) ; 2.18 (d, $^3J_{H3H3'}$ = 10.1 Hz, 1H, CHO*H*) ; 2.58 (m, 2H, CH_3CH_2S) ; 3.80 (s, 3H, OC*H*$_3$) ; 3.92 (ddd, $^3J_{H3F}$ = 20.3 Hz, $^3J_{H3H4}$ = 2.5 Hz, $^3J_{H3H3'}$ = 10.1 Hz, 1H, C*H*CF). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (*C*H$_3$CH$_2$) ; 15.5 and 21.2 ((*C*H$_3$)$_2$CH), 24.0 (CH_3CH_2) ; 29.5 (CH$_3$)$_2$*C*H) ; 53.2 (O*C*H$_3$) ; 77.8 (d, $^2J_{CF}$ = 21.5 Hz, 1C, *C*HCF) ; 105.9 (d, $^1J_{CF}$ = 235.2 Hz, 1C, CH*C*F) ; 168.5 (d, $^2J_{CF}$ = 32.2 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -152.8 (d, $^3J_{HF}$ = 21.2 Hz, 1F, CHC*F*).Anal.Calc. for $C_9H_{17}O_3SF$ (224.30) : C, 48.19 ; H, 7.64 Found C, 47.96 ; H, 7.84 .

Methyl 2-ethylsulfanyl-2-fluoro-3-cyclopentanyl-3-hydroxy-propanoate 8a

At *-78°C*, from **3a** (200 mg, 1.31 mmol) and cyclopentanone (0.12 mL, 1.34 mmol), after purification **8a** was obtained (160 mg, 52%) as unstable product, and must be store at -20°C.

^{1}H NMR ($CDCl_3$) : δ = 1.19 (t, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_3$CH$_2$S) ; 1.4-2.1 (m, 8H, 4xCH_2)) ; 2.4-2.8 (m, 2H, CH_3CH_2S) ; 2.75 (m, O*H*), 3.80 (s, 3H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$) : δ = 14.6 (*C*H$_3$CH$_2$) ; 23.5 and 24.1(*C*H$_2$) ; 24.6 (CH_3CH_2) ; 35.8 and 37.2 (*C*H$_2$) ; 53.1 (O*C*H$_3$) ; 85.5 (d, $^2J_{CF}$ = 22.4 Hz, 1C, *C*CF) ; 106.2 (d, $^1J_{CF}$ = 235.2 Hz, 1C, *C*CF) ; 169.3 (d, $^2J_{CF}$ = 32.3 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -144.7 (s, 1F, CHC*F*). MS : m/z (%) = 236 ([M]$^{+\cdot}$, 3) ; 177 (2) ; 152 (93) ; 151 (66) ; 120 (99) ; 85 (33) ; 59 (41).

Methyl 2-benzylsulfanyl-2-fluoro-3-hydroxy-3-phenyl-propanoate 4c

At -78°C, from methyl 2-fluoro-2-phenylsulfanylacetate **3c** (200 mg, 0.93 mmole) and benzaldehyde (96.5 µL, 0.95 mmole), a diastereomeric mixture of **4c** was obtained in a 56/44 *syn/anti* ratio (^{19}F and ^{1}H NMR). By column chromatography were obtained 53mg (18%) of pure *syn* isomer, 65mg (22%) of a diastereoisomeric mixture and 36mg (12%) of pure *anti* isomer. The *syn* isomer was recristallised in pentane to afford a single cristal suitable for the X-*ray* analysis (mp : 95°C).

At -50°C, from **3c** (214 mg, 1 mmole) and benzaldehyde (150 µL, 1.02 mmole), a diastereomeric mixture of **4c** was obtained in a 68/32 *syn/anti* ratio (^{19}F and ^{1}H NMR), yielded by column chromatography to 165 mg (52%) of diastereomers.

At 0°C, from **3c** (187 mg, 0.9 mmole) and benzaldehyde (93.4 µL, 0.92 mmole), a diastereomeric mixture of **4c** was obtained in a 20/80 *syn/anti* ratio (^{19}F NMR). After purification 140 mg (49%) of

diastereomers were obtained.

syn isomer : ^{1}H NMR ($CDCl_3$) : δ = 2.90 (d, $^3J_{HH}$ = 4.64 Hz, 1H, CHO*H*) ; 3.53 (s, 3H, O*CH*$_3$) ; 3.98 et 3.93 (syst. ABX, $^2J_{HAHB}$ = 13 Hz, $^4J_{HAF}$ = $^4J_{HBF}$ = 1.4 Hz, 2H, C*H*$_2$Ph) ; 5.16 (dd, $^3J_{HF}$ = 17.6 Hz, 1H, *CH*OHCF) ; 7.31 (m, 10H). ^{13}C NMR ($CDCl_3$) : δ = 33.7 (*CH*$_2$Ph) ; 52.9 (O*CH*$_3$) ; 76.3 (d, $^2J_{CF}$ = 22.3 Hz, *C*HOHCF) ; 103.8 (d, $^1J_{CF}$ = 238 Hz, *C*FCH) ; 127.6-129.3,136.1, 136.6 (aromatic*C*), 167.8 (*C*O). ^{19}F NMR ($CDCl_3$) : δ = -153.2 (d, $^3J_{HF}$ = 17.6 Hz, 1F, CHC*F*).*anti isomer* : ^{1}H NMR ($CDCl_3$) : δ = 2.87 (m, 1H, CHO*H*) ; 3.68 (s, 3H, O*CH*$_3$) ; 3.76-3.81 (ABXsyst., $^2J_{HAHB}$ = 12.5 Hz, $^4J_{HAF}$ = $^4J_{HBF}$ = 1.82 Hz, 2H, C*H*$_2$Ph) ; 5.18 (d, $^3J_{HF}$ = 18.5 Hz, 1H, *CH*OHCF) ; 7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) : δ = 33.8 (*CH*$_2$Ph) ; 53.3 (O*CH*$_3$) ; 76.7 (d, $^2J_{CF}$ = 20.35 Hz, *C*HOHCF) ; 103.9 (d, $^1J_{CF}$ = 237.1 Hz, *C*FCH) ; 127.6-129.3, 135.7,136.7 (aromatic*C*) ; 167.9 (d, $^2J_{CF}$ = 31.9 Hz, *C*O). ^{19}F NMR ($CDCl_3$) : δ = -156 (d, $^3J_{HF}$ = 17.6 Hz, 1F, CHC*F*). Anal.Cal. for $C_{17}H_{17}O_3SF$ (320.38) : C, 63.73 ; H, 5.35 Found C, 63.65 ; H, 5.42 .

References and Notes

1. O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc. Chem. Comm.* **1997**, 645-652.
2. Wilkinson, J. A. *Chem. Rev.* **1992,** *92*, 505-519.
3. Welch, J. T. *Tetrahedron* **1987,** *43*, 3123-3197.
4. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995,** *60*, 3107-3111.
5. Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990,** *31*, 7301-7304.
6. McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991,** *113*, 7439-7440.
7. Welch, J. T.; Lin, J. *Tetrahedron* **1996,** *52*, 291-304.
8. Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990,** *31*, 7297-7300.
9. McCarthy, J. R.; Huber, E. W.; Le, T. B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron* **1996,** *52*, 45-48.
10. Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980,** *45*, 3549-3554.
11. Calderon, A.; Font, J.; March, P. D. *Tetrahedron* **1992,** *48*, 5347-5358.
12. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991,** *47*, 7897-7910.
13. Uenishi, J.; Tomaze, H.; Yamato, M. *Tetrahedron Lett.* **1985,** *26*, 3467-3470.
14. Linde, R. G.; Jeronic, L. O.; Danishefsky, S. J. *J. Org. Chem.* **1991,** *56*, 2534-2538.
15. Denis, J. N.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 4111-4112.
16. Shimagaki, M.; Shiokawa, M.; Sugai, K.; Teranaka, T.; Nakata, T. *Tetrahedron Lett.* **1988,** *29*, 659-662.
17. Capet, M.; Cuvigny, T.; Penhoat, C. H.; Julia, M.; Loomis, G. *Tetrahedron Lett.* **1987,** *28*, 6273-6276.
18. Warren, S.; Brownbridge, P. *J. Chem. Soc. Perkin I* **1977**, 2272-2283.
19. Brownbridge, P.; Fleming, I.; Pearce, A.; Warren, S. *J. Chem. Soc. Chem. Comm.* **1976**, 751-752.
20. Allmendinger, T. *Tetrahedron* **1991,** *27*, 4905-4914.
21. Ducep, J. B.; Bildstein, S.; Jacobi, D. *Tetrahedron Lett.* **1996,** *37*, 8759-8762.
22. Fuchigami, T.; Shimojo, M.; Konno, A. *J. Org. Chem* . **1995,** *60*, 3459-3464.
23. a) Brigaud, T.; Laurent, A. *Tetrahedron Lett.* **1990,** *31*, 2287-2290.
    b) Laurent E., Marquet B., Roze C., Ventalon F. *J. Fluorine Chem.* **1998**, *87*, 215-220.
24. McCarthy, J. R.; Peet, N. P.; Letourneau, M. E.; Inbasekaran, M. *J. Am. Chem. Soc.* **1985,** *107*, 735-737.
25. Jouen, C.; Pommelet, J. C. *Tetrahedron* **1997,** *53*, 12565-12574.
26. Jouen, C.; Lasne, M. C.; Pommelet, J. C. *Tetrahedron Lett.* **1996,** *37*, 2413-2416.
27. Iwama, T.; Matsumoto, H.; Kataoka, T. *J. Chem. Soc. Perkin trans 1* **1997**, 835-843.
28. Cousseau, J.; Albert, P. *J. Org. Chem.* **1989,** *.54*, 5380-5382.
29. Pohmakotr, M.; Thisayusta, J. *Tetrahedron Lett.* **1997,** *38*, 6759-6762.
30. Heathcock, C. H. . In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 2; pp. 181-237.
31. Satoh, T.; N. Itoh, K. I. O.; Kitoh, Y.; Yamakawa, K. *Tetrahedron Lett.* **1992,** *33*, 1483-1484.
32. Fujii, A.; Usuki, Y.; Iio, H.; Tokoroyama, T. *Synlett* **1994**, 725-726.
33. X-*Ray* cristallographic data have been performed by M^r L. Toupet (UMR 6626 - Université de Rennes I). The authors have deposited atomic coordinates for these structure with the Cambridge Data Center, 12 Union Road, Cambridge, CB 1EZ, UK.