Pergamon

Tetrahedron, Vol. 52, No. 46, pp. 14631-14640, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00874-5

Nucleophilic Ring Opening of 3-*F*-Alkyl 2,3-Epoxypropanoates. Access to α,β-Difunctional β-*F*-Alkylpropanoates

Marion Lanier, Maurice Le Blanc and Raphaël Pastor*

Laboratoire de Chimie Moléculaire, CNRS URA 426. Université de Nice-Sophia Antipolis.
Faculté des Sciences. Parc Valrose. F-06108 Nice Cedex 2, France.

Abstract: Nucleophilic ring opening of 3-*F*-alkyl 2,3-epoxypropanoates **1** with primary amines or chloride ions leads regioselectively to 2-substituted 3-*F*-alkyl 3-hydroxypropanoates. Azidolysis is not so selective but 2-azido 3-*F*-alkyl 3-hydroxypropanoates **7** are still the major products. With $NaBH_4$ in alcoholic media (EtOH, OcOH) 2-alkoxy 3-*F*-alkyl 1,3-propanediols (**2**=Et, **3**=Oc) are obtained. **Copyright © 1996 Elsevier Science Ltd**

Introduction

The epoxyesters, and especially the glycidates, are important key intermediates in the synthesis of many organic compounds, through the opening of their oxiran ring by nucleophiles[1] like amines[2], azides[3], sulfides[2e,3k,4], carbanions[3a,5], halides[3f,k,6], hydrides[7].

These reactions may be performed in acidic, neutral or basic medium. It is commonly admitted for a long time[8] that the reaction proceeds mainly by a SN^2 mechanism with an anti opening. It begins with the nucleophilic attack on one of the oxiranic carbon atoms (C2 or C3) with inversion of its configuration. In some cases of C2 attack, a product resulting from a syn opening has been also isolated[3l]. The factors influencing the regioselectivity (substrate's structure, reagent's nature, reaction's conditions...) have been investigated very extensively in the hydrocarbon series but, when the alkyl chain of the epoxyester is replaced by a *F*-alkyl chain, the known data are limited to the trifluoromethyl group[2a,3a,9]. Yet the opening of monosubstituted epoxides bearing a long *F*-alkyl chain was found to proceed quite smoothly and used in the preparation of highly fluorinated surfactants[10].

In a previous work[11], describing the preparation of 3-*F*-alkyl 2,3-epoxypropanoates, we pointed out the lack of reactivity of their oxiran ring in acidic medium, as evidenced by their inertia during *p*-toluenesulfonic acid-catalyzed transesterification reactions, and furthermore by the improvement of their purification procedure by chromatography after acidification of the eluent. This behavior, consistent with the low electron density on the oxiranic oxygen due to the close vicinity of both electron-withdrawing *F*-alkyl and ester groups, was also shown by us for the nitrogen atom in the *F*-alkylaziridine-carboxylates[12].

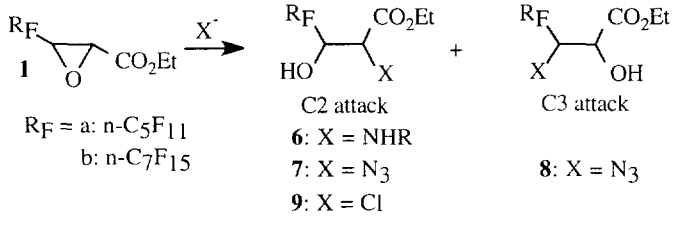
In connection with the main research theme of our Laboratory[13], the synthetic applications of these reactions were the development of new series of polyfunctional bicaudal amphiphiles for biomedical use, through the introduction of long chain alkoxy or alkylamino moieties. The scope of the present work is then

* E-mail pastor@unice.fr -Fax (033) 04 92 07 61 44

restricted to some selected reactions of various nucleophiles such as alcohols, amines, azides, halides onto 3-***F***-alkyl 2,3-epoxypropanoates, in neutral or basic medium. For the aim of more accurate description, our results were compared with the closest examples found in the literature for hydrocarbon analogues.

Results and discussion

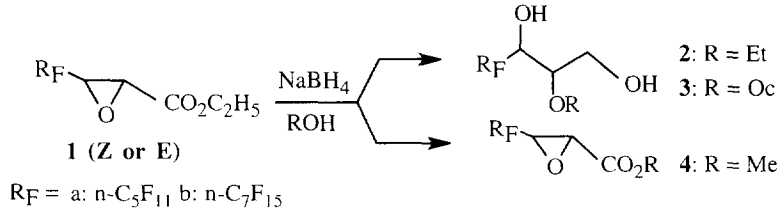
Most of the work presented here may be summarized by the following scheme. It shows that the substitution on carbon C2 is favored and even selective in some cases.



Reduction by $NaBH_4$: When X was H, the reaction followed an unexpected path. These results are presented first because they are very informative upon the mechanism of the epoxide ring opening.

In the hydrocarbon series, the opening of the oxiran ring[7b] or the reduction of the carbonyl function[7a,d,14] may occur, depending on the reaction conditions. In order to prepare 3-*F*-alkyl 2,3-epoxypropan-1-ols, we first tried to treat the epoxyesters **1** by $NaBH_4$ in ethanol, according to a procedure used to reduce selectively the ester groups in hydrocarbon analogues[14].

With our substrates, this selective reduction was no longer observed.



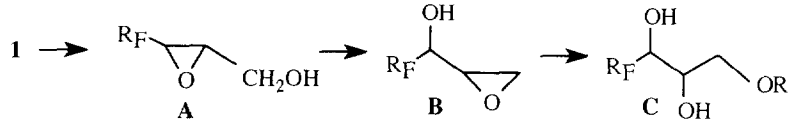
Compound	ROH	C2/C3 attack	Yield*%
1a (Z)	C_2H_5OH	100/0	**2a** 77
1b (Z)	C_2H_5OH	100/0	**2b** 77
1b (E)	C_2H_5OH	100/0	**2b** 77
1b (Z)	$C_8H_{17}OH$	100/0	**3b** 75
1b (Z)	CH_3OH	-	**4b** 95

Table 1: Alcoholic opening of ethyl 3-*F*-alkyl 2,3-epoxypropanoates **1**
* In isolated product.

Thus, after 24h at room temperature, the conversion of **1** was complete and the 1-*F*-alkyl 2-ethoxy 1,3-propanediols **2** were isolated in 77% yield. (Table 1).

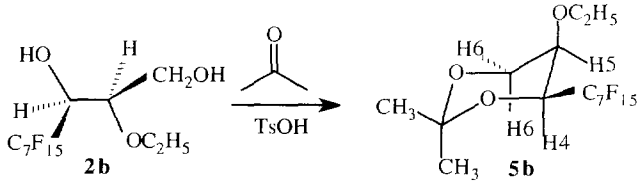
With a higher homologue of ethanol like 1-octanol, the reaction proceeded in a similar way, giving **3**, but when a lower homologue like methanol was used, a quantitative transesterification led to **4** .

These results showed that the reaction may follow a quite different course, depending on the nature of the nucleophile: with the methoxide ion, the epoxide ring is unaffected while the higher alkoxide ions led apparently to a selective substitution on C2.



If the reduction of the ester group to give **A** was the first reaction step, compounds like **B** or **C**, resulting from a Payne rearrangement, may be formed subsequently[3a], but, in our hands, no other fluorinated compound than **2** was detected in the crude reaction mixture. Thus it seems that the first reaction step was the ring opening and the further reduction of the ester function may be made easier, due to the assistance of the hydroxyl group located on C3. We have noticed a similar behaviour in the reduction of β-*F*-alkyl β-ketoesters by $NaBH_4$[11].

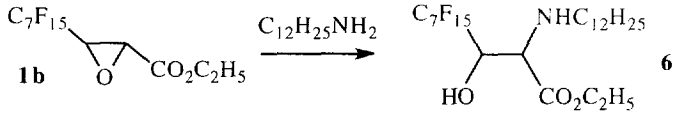
The structure of compounds like **2** was found particularly appropriate to delineate the configurations of carbons 2 and 3 and thus the stereochemistry of the oxiran ring opening. In this intention, **2b** resulting from the oxiran ring opening of **1b(Z)** was transformed to the cyclic acetonide **5b**. On its ^1H NMR spectrum, the signals corresponding to H4 and H5 exhibited a high multiplicity, due to numerous couplings with the nonequivalent fluorine atoms in the vicinal *F*-alkyl chain.



The signal of the methylenic H6 atoms were easier to interpret: the values of their ^3J coupling constants with H5 are almost identical and equal to about 3 Hz. This means that H5 occupies an equatorial position. If one considers that the large *F*-heptyl chain is in an equatorial position and that it forces the entire conformation of the 1,3-dioxacyclohexanic ring, the cis configuration of the ethoxy and *F*-heptyl groups is obvious and results from an anti opening of the oxiran ring in **1b(Z)**[15].

Reaction with amines:

n-dodecylamine: The opening of epoxyacids, esters or amides by ammonia or primary amines in aqueous medium allows a direct acces to α-amino β-hydroxy acids and their derivatives[2a,b,c,g]. The low aqueous solubility of our *F*-alkyl substrates led us to use an organic solvent like THF. After three days under reflux of **1b** with dodecylamine, the conversion ratio was *ca.* 60% and the reaction was completed within six days, leading regioselectively to ethyl 2-(N-*n*-dodecylamino) 3-*F*-alkyl 3-hydroxypropanoate **6**.



diethylamine: In the presence of a Lewis acid catalyst, secondary amines were reported to open the epoxide ring in hydrocarbon series[2d,f,3k]. In analogous conditions or without catalyst, no reaction was

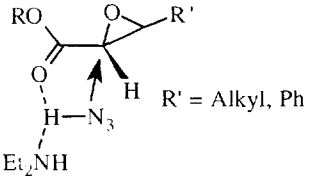
observed between diethylamine and **2** after three days. So it appears that the nucleophilicity of diethylamine is too weak to open the oxiran ring of the *F*-alkylepoxyesters by itself and that the Lewis acid catalytic activation is inoperative.

Reaction with azides: In hydrocarbon series, most of the reactions are performed in water: the yields are good to excellent. With an aryl group at C3, the β-azido esters are obtained selectively, but with an alkyl group, the regioselectivity is poor and may be influenced by the addition of metallic salts, chelating agents,...[3l,16]. The main sources of azide ions are:

-alkaline azides: NaN_3 or LiN_3 used alone or with NH_4Cl[3e,3m]

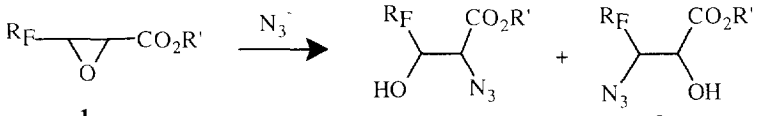
-azides of heteroelements: trimethylsilyl (TMS), tributyl (TBT) and dibutyltin (DBT)[3d,17]

-the HN_3/amine system, known to increase the nucleophilicity of the azide ion and enhance the regioselectivity towards the carbon C2 through a five centered intermediate.[3c]



R' = Alkyl, Ph

The low solubility of our substrates precluding the use of water as solvent, several polar organic solvents were tested (Table 2).



1 **7** **8**

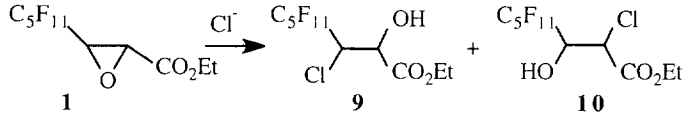
Compound	Method[a]	Solvent	Time	Temperature	Yield %	**7/8** (C2/C3)[b]
1a(E)	A	THF	5 days	reflux	0	-
1a(E)	A	EtOH	1 day	reflux	80	80/20
1a(Z)	A	EtOH	1 day	reflux	60	75/25
1a(E)	C	MeOH	4 days	reflux	80	75/25
1a(E)	B	DMF	5 days	ambient	78	85/15
1b(E)	B	DMF	5 days	ambient	77	88/12
1b(Z)	B	DMF	5 days	ambient	75	90/10

Table 2: Azide ion opening of ethyl 3-*F*-alkyl 2,3-epoxypropanoates **1.** [a]A: NaN_3 alone; B: NaN_3/R_2NH; C: NaN_3/NH_4Cl. [b]The **7/8** ratios (and thus the C2/C3 attack ratio) were determined on the basis of the ^{19}F and ^1H NMR spectra of the crude reaction mixture (cf. experimental part).

In hydrocarbon series, in same conditions, a C2/C3 opening ratio near 60/40 is obtained with C3 alkyl substituted glycidic esters and 100% C3 azidation with C3 phenyl substituted[3c,e,m]. In all cases, the reaction is completed in a few hours (under reflux) or less then one day (room temperature).

For our *F*-alkylepoxyesters the reaction kinetics were comparable in ethanol or DMF whatever their *E* or *Z* configuration and greatly slower than for hydrocarbon analogues in any of the tested methods. No reaction occured in a non dissociating solvent like THF.

Reaction with chloride ion: The conversion of epoxides into halohydrins may be performed by means of various halides of Al, Fe, Sn, Si, P, Cu, Ni, B[6a,c,e,18] often in the presence of additives such as cyclopentadiene, alkoxides, DBU, acetic acid or lithium halides. The $TiCl_4$/LiCl couple, which strongly favored a C3 attack upon 3-alkyl 2,3-epoxyalkanoates under mild conditions, appeared very promising[6c]. Unfortunately, no reaction was observed with **1a** after 24h. However, a slow yet highly regioselective reaction with $AlCl_3$ led exclusively to **9**, besides unchanged **1a**: no Lewis acid-catalyzed isomerisation involving the epoxide ring has occured. Its rather electron-poor nature is in agreement with the hypothesis that its opening is only due to a nucleophilic attack of the chloride ions present in the reaction mixture.



1 **9** **10**

Experimental conditions	Yield %	Selectivity **9/10**
$TiCl_4$ / LiCl / THF / -78°C-> Amb	0	-
$AlCl_3$ / heptane / 25°C / 5 days	49	100/0
$AlCl_3$ / heptane / reflux / 3 days	45	100/0
$AlCl_3$ / THF / reflux / 7 days	20	100/0

Table 3: Reactions with chlorides.

So it appears that when the nucleophile is strong enough, the *F*-alkyl chain favours an attack onto the C2 carbon although the regiospecificity of these reactions was not total with the azide ion. The low electronic density on the oxiranic oxygen makes any Lewis acid catalysis ineffective.

NMR:

The ^1H NMR spectra of all products obtained from 3-*F*-alkyl 2,3-epoxypropanoates exhibit similar patterns. This observation is also valid for their ^{19}F and ^{13}C NMR spectra. So, the regiospecificity of their oxiranic ring opening is identical for all the nucleophiles tested, indicating an attack to the C2 carbon.

^1H NMR: The signal corresponding to the hydrogen of the hydroxy group at C3 appears as a doublet with $^3J_{HH}$=8Hz. The hydrogen bound to C3 - *i.e.* vicinal to the *F*-alkyl chain - appears always as a broad doublet, with $^3J_{HF}$=20Hz, near 5 ppm. Both signals are modified on dropping D_2O in NMR tube. The hydroxy signal collapses and the C3 bound hydrogen becomes a doublet of poorly resolved triplets, $^3J_{HF}$=20hHz and $^3J_{HH}$ and $^3J_{HF}$=2-4Hz.

^{19}F NMR: The two fluorines of the $CF_2\alpha$ are non equivalent and their signals appear at -120 and -127 ppm as a AB system with $^2J_{FF}$=280 Hz. Those of the $CF_2\beta$ also appear as a AB system centered at -126/-127 ppm.

^{13}C NMR: The signal due to the C3 carbon is easy to assign: it appears as a quadruplet near 68 ppm, with two different $^2J_{CF}$ coupling constants. The C2 signal is a broad triplet near 59 ppm.

The different $^3J_{HF}$ and $^2J_{CF}$ observed for the two fluorine atoms of the $CF_2\alpha$ mean that they are not only non equivalent but they are also very different in conformational position and in electronic densities.

The location of an asymmetric center near these two fluorine atoms is not sufficient to explain these observations. The hydroxy function might also perturb the electronic circulation on one of the neighbouring fluorine atoms through an hydrogen bonding.

Conclusion

The reaction of some selected nucleophiles upon 3-*F*-alkyl 2,3-epoxypropanoates, while proceeding slower than in hydrocarbon series, showed a much higher regioselectivity. The substitution on the α carbon is the only detected process with primary amine, alkoxide or halide ions. With the azide ion, this selectivity still remained marked. Although more reactive than their aziridino analogues[12], these epoxyesters appeared unsensitive towards electrophiles such as Lewis acid catalysts, but nucleophilic reactions may lead to various series of polyfunctional β-*F*-alkyl β-hydroxy α-substituted propanoates of well-defined structures. The preparation of several families of such synthons and their use in the preparation of more complex molecules obeying to rigorous chemical, physicochemical or biological constraints is now under investigation.

Experimental

General

Gas chromatography was performed on a DELSI instrument (FID detector) fitted with a 3mx1/4in. column packed with 30% SE30 on Chromosorb. All GC analysis were performed as follows: 120°C for 5 min, then heating at 5 °C min^{-1} up to 200°C. Infrared spectra were obtained as KBr pellets or films on a Bruker IFS spectrometer. ^{1}H (200MHz), ^{13}C (51,2MHz) (internal reference Me_4Si) and ^{19}F (188,3MHz) (internal reference $CFCl_3$, negative for upfield shifts) NMR spectra, all samples in $CDCl_3$ solution, were recorded on a Bruker AC 200 spectrometer. Combined gas chromatography/mass spectrometry were performed with an R10 Ribermag L10 instrument, EI (70ev).

2-alkoxy 3-F-alkyl 1,3-propanediols.

Typical procedure: 0.4 mmole of $NaBH_4$ and 0.3 mmole of ethyl 3-*F*-alkyl 2,3-epoxypropanoate **1** in 5ml of distilled ethanol were stirred overnight at room temperature. Then the mixture was hydrolyzed with 10ml of 10% aqueous HCl, extracted with diethyl ether (3x30ml) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the slighty yellow residual liquid was purified by chromatography on silica gel (Eluent: pentane/diethyl ether 3/7) (Yield:77%).

Products (anti or syn configurations) from **1(Z)** or **1(E)** oxirane ring opening have same IR and very similar ^{1}H and ^{13}C NMR spectra. Compounds **2a** and **2b** with different *F*-alkyl chains differ only by their ^{19}F NMR spectra.

2-ethoxy 3-F-pentyl 1,3-propanediol (**2a from 1a(E)**): mp= 71-73°C. Analysis: (calc.) found: C (30.93) 30.92, H (2.83), 2.74. IR (ν cm^{-1}, KBr): 3500-3100 (ν_{OH}), 1300-1100 (ν_{CF}). ^{1}H NMR: 1.17 (t, $^{3}J_{HH}$=7Hz, 3H, C<u>H</u>$_3$), 1.92 (m, CH_2-O<u>H</u>), 3.21 (d, $^{3}J_{H\text{-}OH}$=8.2Hz, O<u>H</u>), 3.55-3.80 (m, 5H, C<u>H</u>OEt, 2C<u>H</u>$_2$O) , 4.09 (dd, $^{3}J_{HF}$=23.5Hz, $^{3}J_{H\text{-}OH}$=8.2Hz, 1H, C<u>H</u>-CF_2). ^{13}C NMR: 15.48 (<u>C</u>H_3), 61,96 (<u>C</u>H_2), 67.43 (<u>C</u>H_2-OH), 68.27 (q, $^{2}J_{CF}$=28.9 and 21.8Hz, <u>C</u>H-OH), 74.88 (<u>C</u>H-O). ^{19}F NMR: -81.1 (CF_3), -122.4 ($CF_2\gamma$), -123.1 ($CF_2\beta$), -119.1/-120.5/-127.5/-128.6 (J_{AB}= 280Hz, $CF_2\alpha$), -126.5 ($CF_2\omega$).

2-ethoxy 3-F-heptyl 1,3-propanediol (**2b from 1b(Z)**): Analysis (calc.) found: C (29.51) 29.29, H (2.24) 2.27. ^{19}F NMR: -81.1 (CF_3), -123.1/-122.4 ($4CF_2$), -119.0/-120.6/-127.2/-128.7 (J_{AB}=280Hz, $CF_2\alpha$), -126.5 ($CF_2\omega$).

2-octyloxy 3-F-heptyl 1,3-propanediol **4b**: mp = 77-79°C. IR (ν cm^{-1}, KBr) : 3600-3200 (ν_{OH}), 1300-1100 (ν_{CF}). ^1H NMR : 0.75 (t, $^3J_{HH}$=7Hz, 3H, CH_3), 1.10-1.40 (m, 12H, 6 CH_2); 1.9 (l, 1H, O<u>H</u>), 3.1-3.2 (d,$^3J_{H\text{-}OH}$=8.2Hz, O<u>H</u>), 3.52-3.75 (m, 5H, C<u>H</u>$_2$-C<u>H</u>, C<u>H</u>$_2$-O), 4.08-4.22 (m, 1H, C<u>H</u>-CF_2). ^{19}F NMR: -81.2 (CF_3), -119.6/-121.2/-127.7/-129.3 (J_{AB}=275Hz, $CF_2\alpha$), -122.4/-123.2/-123.7 ($4CF_2$), -126.6 ($CF_2\omega$). (Signals at 1.9 and 3.15 ppm collapse when D_2O is added.)

4-F-heptyl 5-ethoxy 2,2-dimethyl 1,3-dioxacyclohexane **5**. 420 mg (0.9 mmole) of **2b**, 200 mg of PTS in 20ml of 2,2-dimethoxypropane were stirred 2 days at room temperature. The mixture was hydrolyzed with 50ml of water, then extracted with diethyl ether (3x30ml) and dried over Na_2SO_4. After solvent evaporation under reduced pressure, the residual viscous liquid was purified by chromatography on silica gel (Eluent: pentane/diethyl ether 3/7) (Yield: 250mg, 55%). ^1H NMR: 4.48 (m, 1H, H2), 3.94 (2H, dedoubled AB system, $^2J_{H6H6'}$=12Hz, $^3J_{H6H5}$=$^3J_{H5H6'}$=2.5-2.8Hz, C<u>H</u>$_2$), 3.44 and 3.4 (3H, C<u>H</u>OEt and OC<u>H</u>$_2$-CH_3), 1.42 (s, 3H, C<u>H</u>$_3$), 1.39 (s, 3H, C<u>H</u>$_3$), 1.15 (q,3H, C<u>H</u>$_3$). ^{13}C NMR 15.28, 18.7, 28.28 (3 CH_3), 62.5 broad(CH), 65.52(CH_2), 65.65 (CH_2), 69.34 (t,$^2J_{CF}$= 24Hz), 97.5 (Cquat).

Reaction with n-dodecylamine

Ethyl 3-hydroxy 2-(N-n.dodecylamino) 3-F-pentylpropanoate. A mixture of 0.3 mmole (115mg) of ethyl 3-*F*-pentyl 2,3-epoxypropanoate **1a(Z)** and 1 mmole (185mg) of dodecylamine in 30ml of anhydrous THF was heated under reflux. The evolution of the reaction was monitored by gas chromatography. Seven days later, after total disappearing of the epoxypropanoate, the reaction was allowed to return to room temperature, hydrolyzed by 40ml of diluted HCl and extracted with diethyl ether (3x30ml). The organic phases were dried over Na_2SO_4 and concentrated under vacuum. The residual yellow solid was purified by chromatography on silica gel (Eluent: pentane / diethyl ether 95/5) yielding 140mg (80%) of **6b**. mp=94-96°C. IR (ν cm^{-1}, KBr) 3600-3200 ($\nu_{OH,NH}$), 1740 (ν_{CO}), 1300-1100 (ν_{CF}). ^1H NMR: 0.75-1.70 (m, 26H), 2.47-2.75 (m, 3H, N<u>H</u>, NC<u>H</u>$_2$), 3.50 (d $^3J_{H\text{-}H}$=4.7Hz, C<u>H</u>N), 4.07-4,13 (m, 2H, C<u>H</u>OH, C<u>H</u>$_2$O). ^{13}C NMR: 162.56(CO), 67.64 (dd, $^2J_{CF}$=20.6Hz, $^2J_{CF}$=21.0Hz, <u>C</u>3), 62.33 (<u>C</u>H$_2$), 58.6 (d, $^3J_{CF}$=7Hz, <u>C</u>2), 48.75, 23.29 to 31.91 (9C), 14.07, 13.53 (<u>C</u>H$_3$). ^{19}F NMR: -81.2 (CF_3), -122.6 ($CF_2\gamma$), -121.4/-123.1/-123.5/-125.1 (J_{AB}=310Hz, $CF_2\beta$), -119.5/-120.6/-128.0/-129.4 (J_{AB}=287Hz, $CF_2\alpha$), -126.7 ($CF_2\omega$).

Reaction with azides:

Method A: 0.7 mmole of ethyl 3-*F*-alkyl 2,3-epoxypropanoate and 3.5 mmoles of NaN_3 in 20ml of EtOH are stirred one day on reflux. The disappearing of the epoxyester is monitored by GC. After return at room temperature the reaction mixture was extracted with diethyl ether (3X30ml). The extracts were washed, dried over Na_2SO_4 and concentrated under vacuum. A chromatography on silica gel (Eluant: $CHCl_3$ or Et_2O/Hexane 50/50) of the residue did not allow us to separe ethyl 3-hydroxy 2-azido 3-*F*-alkylpropanoate (**7**) from ethyl 2-hydroxy 3-azido 3-*F*-alkyl propanoate (**8**). Their relative proportions were established on the basis of the HO signals in ^1H spectra and $CF_2\alpha$ signals in ^{19}F NMR spectra of their mixture.

Method B: 0.3 mmole of **1** and 1.2 mmoles of 60ml of a DMF solution of Et_2NH-HN_3 (from 45 mmoles (5g) of Et_2NH.HCl and 45 mmoles (3g) NaN_3 in 200ml of DMF)[3c] are stirred at room temperature. The

disappearing of the epoxyester was followed by GC. After 5 days, the reaction mixture is treated by usual workup.

Method C: 0.3 mmole of **1**, 1.2 mmoles of NaN_3 and 0.3 mmole of NH_4Cl in 20ml of MeOH are stirred 4 days on reflux. After return at room temperature the mixture is treated by usual workup.

Ethyl 2-azido 3-hydroxy 3-F-pentylpropanoate (**7a**) *and Ethyl 3-azido 2-hydroxy 3-F-pentyl propanoate* (**8a**): From 270 mg of **1a(E)**, the method C afforded 122 mg of a 76/24 mixture of **7a** and **8a**. (based on the relative area of their ^1H NMR signals downfield from 4.4 ppm. and of their $CF_{2\alpha}$ signals in the ^{19}F NMR spectrum). Analysis: (calc.) found: C (28.12) 28.06, H (1.89) 1.83, N (9.84) 9.92. IR (ν cm^{-1}, KBr) 3600-3300 (ν_{OH}), 2129 (ν_{N3}) 1741 (ν_{CO}) 1300-1100 (ν_{CF}).

Ethyl 2-azido 3-hydroxy 3-F-pentylpopanoate (**7a**). ^1H NMR: 1.27 (t, $^3J_{H-H}$=7.1Hz, CH_3), 3.15 (d $^3J_{H-H}$=8Hz, O<u>H</u>), 4.1 (d large,$^3J_{H-H}$=4.2Hz, C<u>H</u>N_3), 4.26 (q,$^3J_{H-H}$=7.1Hz, C<u>H</u>$_2$), 4.69 (After D_2O addition, the signal at 3.15 ppm disappears and the signal at 4.69 ppm becomes a broad doublet of triplets, $^3J_{HF}$=20.2Hz, $^3J_{H-H}$ and $^3J_{HF}$=2.6Hz, 1H, C<u>H</u>OH).^{13}C NMR: 167.41(CO), 68.9 (dd, $^2J_{CF}$=21Hz, $^2J_{CF}$=21.5Hz, C3), 63.23 (<u>C</u>H_2) 60.74 (d, $^3J_{CF}$=7Hz, C2), 13.95 (<u>C</u>H_3). ^{19}F NMR: -81.3 (CF_3), -117.6/-119.1/-125.0/-126.5 (J_{AB}=285Hz, $CF_2\alpha$), -123.2/-123.4 ($2CF_2$), -126.7 ($CF_2\omega$).

Ethyl 3-azido 2-hydroxy 3-F-pentylpropanoate (**8a**). ^1H NMR: 1.27 (t, $^3J_{H-H}$=7.1Hz, CH_3), 3.75 (d $^3J_{H-H}$=8Hz, O<u>H</u>), 4.11 (d large,$^3J_{H-H}$=4.2Hz, C<u>H</u>OH), 4.28 (q,$^3J_{H-H}$=7.1Hz, C<u>H</u>$_2$), 4.55 (dt large, $^3J_{HF}$=20Hz, $^3J_{H-H}$ and $^3J_{HF}$=3.6Hz, 1H, C<u>H</u>N_3). On D_2O addition, the signal at 3.75 ppm disappears. ^{13}C NMR: 167.72(CO), 69.41 (dd, $^2J_{CF}$=21Hz, $^2J_{CF}$=20.7Hz, C3), 62.99 (<u>C</u>H_2), 59.98 (d, $^3J_{CF}$=7Hz, C2), 13.81 (<u>C</u>H_3). ^{19}F NMR: -81.3 (CF_3), -118.3/-119.8/-125.9/-127.4 (J_{AB}=283Hz, $CF_2\alpha$), -123.2/-123.4 ($2CF_2$), -126.7 ($CF_2\omega$).

Ethyl 2-azido 3-hydroxy 3-F-heptylpropanoate (**7b**) *and Ethyl 3-azido 2-hydroxy 3-F-pentyl propanoate* (**8b**). From 150 mg of **1b(Z)** , with protocol B, we obtained 120 mg (75%) of a **7b-8b** mixture (90/10 on the integration of the ^1H NMR signals). Analysis: (calc.) found: C (27.34) 27.12, H (1.53) 1.47, N (7,97) 8.12. IR: id **7a, 8a**

Ethyl 2-azido 3-hydroxy 3-F-heptylpopanoate (**7b**). ^1H NMR: 1.27 (t, $^3J_{H-H}$=7.1Hz, 3H, CH_3), 2.95 (d $^3J_{H-H}$=9.1Hz, 1H, O<u>H</u>), 4.26 (q,$^3J_{H-H}$=7.1Hz, 2H, C<u>H</u>$_2$), 4.47 (large,$^3J_{H-H}$=4.2Hz, 1H, C<u>H</u>N_3), 4.76 (dt large, J = 21.5Hz and 4Hz) (After D_2O addition, the signal at 3.15 ppm disappears and the signal at 4.69 becomes a broad doublet, $^3J_{HF}$=20.1Hz, 1H, C<u>H</u>OH).^{13}C NMR: 167.6 (CO), 68.9 (dd, $^2J_{CF}$=21Hz, $^2J_{CF}$=23Hz, C3), 67.07 (<u>C</u>H_2) 60.79 (d, $^3J_{CF}$=7Hz, C2), 13.55 (<u>C</u>H_3). ^{19}F NMR: -81.3 (CF_3),-117.6/-119.1/-125.0/-126.5 (J_{AB}=285Hz, $CF_2\alpha$), -123.0/-123.5 ($4CF_2$), -126.6 ($CF_2\omega$).

Ethyl 2-azido 3-hydroxy 3-F-heptylpropanoate (**8b**). ^1H NMR: 1.25 (t, $^3J_{H-H}$=7.1Hz, 3H, CH_3), 3.7 (d $^3J_{H-H}$=9.1Hz, 1H, O<u>H</u>), 4.26 (q,$^3J_{H-H}$=7.1Hz, 2H, C<u>H</u>$_2$), 4.12 (d,$^3J_{H-H}$=4.2Hz, 1H, C<u>H</u>OH), 4.6 (d large, J = 21Hz, 1H, C<u>H</u>N_3).

Reaction with chloride ion:

Ethyl 2-chloro 3-hydroxy 3-F-pentylpropanoate: **9a**

In a Schlenk's tube, under an inert atmosphere, 0.26 mmole of 3-*F*-pentyl 2,3-epoxypropanoate **1a(Z)** and 0.29 mmole of $AlCl_3$ are placed in 50ml distilled hexane. This mixture was stirred at room temperature 6 days over. After hydrolysis and extraction with diethyl ether, the organic fractions were washed and dried over Na_2SO_4 and concentrated under reduced pressure; the crude residual liquid (about 50/50 mixture of **1a(Z)** and **9a**, on GC and ^1H NMR spectrum) was purified by chromatography on silica gel (Eluent: pentane/Et_2O 9/1).

We obtained 0,52g (yield 49%) of **9a**, as a syrupous yellow liquid. IR (ν cm^{-1}, KBr) 3600-3300 (ν_{OH}), 1740 (ν_{CO}), 1300-1100 (ν_{CF}). ^1H NMR: 1.36 (t, $^3J_{H-H}$=7Hz, CH_3), 3.12 (d $^3J_{H-H}$=8.7Hz, O<u>H</u>), 4.21 (q, $^3J_{H-H}$ =7Hz, C<u>H</u>$_2$), 4.67 (d, $^3J_{H-H}$=4.5Hz, 1H, C<u>H</u>Cl), 4.78 (m -after addition of D_2O it becomes a broad dd, $^3J_{HF}$=19.1Hz, $^3J_{H-H}$=4.5Hz, 1H, C<u>H</u>OH). ^{13}C NMR: 166.15(CO), 68.95 (dd, $^2J_{CF}$=20.6Hz, $^2J_{CF}$=21.0Hz, C3), 67.25 (<u>C</u>H$_2$), 55.76 (d, $^3J_{CF}$=7Hz, C2), 13.54 (<u>C</u>H$_3$). ^{19}F NMR: -81.2 (CF_3), -118.2/-119.7/-125.7/-127.2 (J_{AB}=283Hz, $CF_2\alpha$), -122.9 ($CF_2\beta$), -123.3 ($CF_2\gamma$), -126.6 ($CF_2\omega$). Mass ($C_{10}H_8ClF_{11}O_3$ M=422, 420) m/e (%): 395 (3), 393 (9), 385 (1) (M^+-Cl), 377 (3), 375(7) (M^+-OEt), 357 (10)(M^+-Cl-28), 349 (3), 347 (9) (M^+-CO_2Et), 131 (6), 119 (7), 111 (9), 71 (10), 69 (10), 58 (22), 57 (100), 56 (95), 55 (18), 49 (10), 45 (12), 43 (31), 42 (36), 41 (97).

Acknowledgements: We wish to thank ATOCHEM for the gift of the starting *F*-alkylated products and the Centre National de la Recherche Scientifique and the Ministère de la Recherche et de la Technologie for their financial support.

References

1 Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539-1650.

2 a) Walborsky, H. M.; Baum, M. E. *J. Amer. Chem. Soc.* **1958**, *80*, 187-192. b) Liwschitz, Y.; Rabinshon, Y.; Perera, D. *J. Chem. Soc. Chem. Commun.* **1962**, 1116-1119. c) Kato, K.; Saino, T.; Nishizawa, R.; Takita, T.; Umezawa, H. *J. Chem. Soc.* **1980**, 1618-1621. d) Grosjean, F.; Huche, M.; Larcheveque, M.; Legendre, J. J.; Petit, Y. *Tetrahedron* **1994**, *50*, 9325-9334. e) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320-4323. f) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560-1563. g) Caldwell, C.G.; Bondy, S.S. *Synthesis* **1990**, 34-36.

3 a) Von Dem Bussche-Hunnefeld, C.; Seebach, D. *Chem. Ber.* **1992**, *125*, 1273-1281. b) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790-791. c) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667-670. d) Saito, S.; Yamashita, S.; Nishikawa, T.; Yokoyama, Y.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 4153-4156. e) Legters, J.; Thijs, L.; Zwanenburg, B. *Rec. Trav. Chim.-j. Roy. Neth. Chem.* **1992**, *111*, 1-15. f) Gou, D. M.; Liu, Y. C.; Chen, C. S. *J. Org. Chem.* **1993**, *58*, 1287-1289. g) Denis, J. N.; Correa, A.; Greene A. E. *J. Org. Chem.* **1990**, *55*, 1957-1959. h) Denis, J. N.; Greene A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 45-56. i) Corey, E. J.; Choi, S. Y. *Tetrahedron Lett.* **1991**, *32*, 2857-2860. j) Chatterjee, A.; Williamson, J. S.; Zjawiony, J. K.; Peterson, J. R. *Bioorg. Medicinal Chem. Lett.* **1992**, *2*, 91-94. k) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696-5704. l) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *51*, 13409-13422. m) Legters, J. ; Van Dienst, E.; Thijs, L.; Zwanenburg, B. *Rec. Trav. Chim.-J. Roy. Neth. Chem.* **1992**, *111*, 69-74.

4) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323-4334.

5 a) Petit, Y.; Sanner, C.; Larcheveque, M. *Synthesis* **1988**, 538. b) Onaka, M.; Ohta, A.; Sugita, K.; Izumi, Y. *Applied Catalysis A - General* **1995**, *12*, 203-216. c) Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 1983-1985. d) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477-4480.

6 a) Thijs, L.; Cillissen, P.J.M.; Zwanenburg, B. *Tetrahedron* **1992**, *48*, 9985-9990. b) Tamura, M.; Shibakami, M.; Arimura, T.; Kurosawa, S.; Sekiya, A. *J. Fluorine Chem.* **1995**, *70*, 1-3. c) Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett* **1992**, 204-206. d) Otsubo, K; Inanaga, J; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435-4436. e) Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401-13408.

7 a) Rao, A. V. R.; Rao, S. P.; Bhanu, M. N. *J. Chem. Soc. Chem. Commun.* **1992**, 859-860. b) Mohrig, J.R.; Vreede, P.J.; Schultz, S.C.; Fierce, C.A. *J. Org. Chem.* **1981**, *46*, 4655-4658. c) Lanier, M.; Pastor, R.; *Tetrahedron Lett.* **1995**, *36*, 2491-2492. d) Corsano, S.; Piancatelli, H. *J. Chem. Soc. Chem. Commun.* **1971** 1106.

8 a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, 737-799. b) Bartok, M.; Lang, K. L., in "*Small Ring Heterocycles*", Part 3, A. Hassner (ed), Wiley-Interscience, New York, **1985**, p. 115.

9 a) Yamazaki, T.; Okamura, N.; Kitazume, T. *Tetrahedron Asymmetry* **1990**, *1*, 521-524. b) Ramachandran, P. V.; Gong, B.; Brown, H.C. *J. Org. Chem.* **1995**, *60*, 41-46.

10 a) Coudures, C.; Pastor, R.; Szonyi, S.; Cambon, A. *J. Fluorine Chem.* **1984**, *24*, 105-115. b) Plenkiewicz, H; Dmowski, W *J. Fluorine Chem.* **1989**, *45*, 389-400. c) Nivet, J. B.; Le Blanc, M.; Haddach, M.; Lanier, M.; Pastor, R. ; Riess, J. G. *New J. Chem.* **1994**, *18*, 861-869.

11) Lanier, M.; Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron Lett.* **1993**, *34*, 2469-2472.

12 a) Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron Lett.* **1990**, *31*, 1989-1990. b) Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron* **1993**, *49*, 4627-4638.

13a) Riess, J. G. *Fluorine in Medicine in the 21st Century*, Banks R.E., Lowe K.C. Eds, Chap 20, Rapra, Shawbury, **1994**. b) Riess, J. G. *New. J. Chem.* **1995**, *19*, 891-909.

14) Mauger, J.; Robert, A. *Tetrahedron* **1988**, 44, 2493-2502

15) Cai J.; Davies A.G.; Schiesser C.H. *J. Chem. Soc., Perkin Trans 2* **1994**, 1151-1156.

16) Legters, J.; Thijs, L.; Zwanenburg, *Tetrahedron* Lett. **1989**, *30*, 4881-4884.

17) Saito, S.; Nishikawa, T.; Yokoyama, Y; Moriwake, T. *Tetrahedron Lett.* **1990**, *31*, 221-224

18) Shibata, I.; Yoshimura, N.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1992**, *33*, 7149-7152.

(*Received in Belgium* 4 *July* 1996; *accepted* 23 *September* 1996)