Tetrahedron Letters, Vol. 34, No. 15, pp. 2469-2472, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Stereoselective Synthesis of *F*-alkyl α,β-Unsaturated Esters and their Epoxidation

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Abstract: Strong electrophilic Z and E 3-*F*-alkyl 2-propenoates have been prepared stereoselectively. Their extremely difficult epoxidation has been achieved with retention of stereochemistry using t-BuO_2Li, leading to *F*-alkyl glycidic esters, which are useful building blocks for the synthesis of new amphiphiles.

Highly amphiphilic molecules bearing a *F*-alkyl chain are needed for the formation of stable fluorocarbon emulsions or vesicles for biomedical uses[1]. Further improvement in the control of the physical characteristics of these systems and understanding of their biological effects imply the control of the stereochemistry of the *F*-alkylated components. 3-*F*-alkyl 2,3-epoxy propenoates are a valuable class of compounds for the synthesis of such molecules.

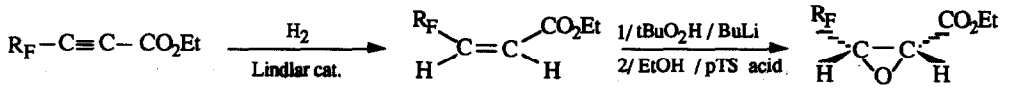
Substituted glycidic derivatives are commonly used as building blocks for the synthesis of polyols and polyfunctional compounds[2]. In the hydrocarbon series, they are currently obtained by numerous methods of epoxidation of α,β-unsaturated esters and acids[3-8]. On the other hand, very few *F*-alkyl glycidic esters are reported in the literature. While *F*-alkenes are easily epoxidized by hypohalogenated acids in acetonitrile[9], *F*-alkyl substituted alkenes are not. The epoxidation of R_F-CH=CH_2 requires several steps[10]. Another route, developped by Seebach, consists in the ring closure of 4,4,4-trifluoro 3-hydroxy butanoates with the LDA/I_2 system to give the epoxide[11]. So far, direct epoxidation of 3-*F*-alkyl 2-propenoates has never been reported.

Perfluoroalkyl propenoates are often obtained as mixtures of E and Z isomers, either by addition of perfluoroalkyl radicals to acrylates[12] or by deshydratation of β-hydroxyesters[13]; most of these alkenes are short *F*-alkyl chain compounds. Recently, Takacs has reported a convenient two-carbon elongation of esters using a one step reduction-olefination sequence[14]. This method was adapted by Burton to the synthesis of α-fluoro α,β-unsaturated esters, including short chain *F*-alkyl esters[15].

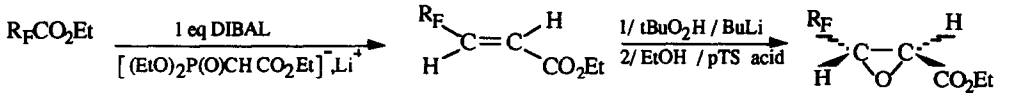
In this paper, we report the stereoselective synthesis of *F*-alkyl α,β-unsaturated esters and their epoxidation. The Z α,β-unsaturated esters **1** were prepared stereoselectively by catalytic hydrogenation of the corresponding alkynes, as previously described[16], in 90 % yield (Z/E ratio = 100/0). For the synthesis of the E isomer, Takacs' procedure was successfully applied to the conversion of long chain *F*-alkyl esters into α,β-unsaturated esters with high stereoselectivity. The *F*-alkyl aldehyde, produced in situ from the half-reduction of the *F*-ester using 1 eq. of diisobutylaluminium hydride (DIBAL), reacts with the lithium phosphono

acetate $[(EtO)_2P(O)CHCO_2Et]^-\ Li^+$ via a Horner-Wadsworth-Emmons process to give predominantly the E isomer **2**[17].

The structure of the alkenes **2** was ascertained by ^1H, ^{13}C and ^{19}F NMR spectroscopy[18]. The Z/E ratio was determined by ^{19}F NMR analysis of the reaction mixture and confirmed by GPC. The yields are given for the major isomer after purification.



1a : 76% (Z : 100) **3a : 60%**
1b : 85% (Z : 100) **3b : 62%**



R_F = a: C_5F_{11}, b: C_7F_{15}

2a : 53% (Z/E : 5/95) **4a : 68%**
2b : 56% (Z/E : 4/96) **4b : 70%**

α,β-Unsaturated esters are known to be difficult to epoxidize due to the lack of electron density at the double bond. In the case of **1a,b** and **2a,b** this difficulty is increased by the presence of the *F*-alkyl chain. Actually, we have attempted to oxidize the Z-alkenes **1a,b** and E-alkenes **2a,b** with a variety of epoxidation methods used both in the hydrocarbon[3-8] and in the fluorinated[9] series, but all the methods investigated failed. The starting products were recovered along with some degradation products.

Only the method recommended by Clark and al[19] was successful. It is a stereospecific epoxidation procedure for alkenes with strong acceptor groups[20]. Lithium t-butylhydroperoxide, formed in situ from anhydrous $tBuO_2H$ and BuLi in hexane[21], reacts at -78°C with the 3-*F*-alkyl 2,3-propenoates **1** and **2**. In these conditions the alkenes were quantitatively epoxidized, but significant amounts of by-products, resulting from the transesterification of the epoxyester by the lithium n-butoxide and t-butoxide, were detected. A study of the reaction kinetics allowed us to establish that the lowest amount of transesterification is found for 4 hours of reaction. Mixed epoxyesters were then ethanolysed with *p*-toluenesulfonic acid to give the pure epoxyethyl esters[22]. In these reaction conditions, the initial configuration of the alkene is retained, as shown by the NMR data[23]. We could therefore obtain both epoxides separately.

In summary, we have stereoselectively prepared both the Z and E perfluoroalkyl propenoates by hydrogenation of the corresponding alkynes, and by a Horner-Wadsworth-Emmons procedure applied to the perfluoroalkyl ester, respectively. The reaction of the electron-poor double bonds with $tBuO_2H$ gave the epoxide with retention of configuration.

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

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17. In a typical procedure, 60 mmol. of n-butyl lithium in hexane was added to a cooled solution (- 78°C) of 60 mmol. of $(EtO)_2P(O)CH_2CO_2Et$ in anhydrous THF. To the resulting solution, 50 mmol. of the *F*-ester was added in one portion. Then, 50 mmol. of DIBAL was added dropwise and the temperature was kept at -78°C during the addition. The mixture was allowed to warm up to room temperature over 5 hours, and was then quenched with HCl 10%. After the usual workup, the E isomer was isolated by chromatography on silica gel (pentane/ether 8:2).
18. The structural data on the alkenes **1** and **2** were determined by ^1H (internal reference TMS, 200 MHz), ^{13}C (internal reference TMS, 50 MHz) and ^{19}F (internal reference $CFCl_3$, 188 MHz) NMR, all samples in $CDCl_3$.

1. ^{1}H NMR : 1.31 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3); 4.27 (q, 2H, $^3J_{HH}$ = 7 Hz, CH_2); 5.90 (broad q, 1H, $^3J_{HH\ cis}$ = 12.9 Hz, $^3J_{HF}$ = 13 Hz, CF_2-CH=); 6.45 (dt, 1H, $^3J_{HH\ cis}$ = 12.9 Hz, $^4J_{HF}$ = 2 Hz, =CH-CO). ^{13}C NMR : 13.68 (CH_3); 61.69 (CH_2); 122.68 (t, $^3J_{CF}$ = 24.3 Hz, CF_2-CH=); 132.02 (t, $^4J_{CF}$ = 6.0 Hz, =CH-CO); 163.93 (CO). ^{19}F NMR **1a** : -81.4 (CF_3); -110.2 ($CF_2\alpha$); -122.2 ($CF_2\beta$); -123.3 ($CF_2\gamma$); -126.6 ($CF_2\omega$). ^{19}F NMR **1b** : -81.6 (CF_3); -110.3 ($CF_2\alpha$); -122.1 ($CF_2\beta$); -122.2 (CF_2); -123.5(2 CF_2); -126.8 ($CF_2\omega$).

2. ^{1}H NMR : 1.34 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3); 4.29 (q, 2H, $^3J_{HH}$ = 7 Hz, CH_2); 6.54 (dt, 1H, $^3J_{HH\ trans}$ = 16 Hz, $^4J_{HF}$ = 1.9 Hz, =CH-CO); 6.83 (dq, 1H, $^3J_{HH\ trans}$ = 16 Hz, $^3J_{HF}$ = 11.7 Hz, CF_2-CH=). ^{13}C NMR : 14.05 (CH_3); 61.83 (CH_2); 130.68 (t, $^2J_{CF}$ = 23.8 Hz, CF_2-CH=); 131.14 (t, $^3J_{CF}$ = 10.2 Hz, =CH-CO); 163.65 (CO). ^{19}F NMR **2a** : -81.4 (CF_3); -114.1 ($CF_2\alpha$); -122.9 ($CF_2\beta$); -123.9 ($CF_2\gamma$); -126.8 ($CF_2\omega$). ^{19}F NMR **2b** : -81.5 (CF_3); -114.2 ($CF_2\alpha$); -122.1 ($CF_2\beta$); -122.7/ -123.4/-123.8 (3CF_2); -126.8 ($CF_2\omega$).

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22. In a typical procedure, 3.2 mmol. of $tBuO_2H$ in anhydrous toluene was added to a cooled solution (- 78°C) of 3.2 mmol. of BuLi in anhydrous THF. After 1 hour of stirring at -78°C, 2.7 mmol of 3-*F*-alkyl 2,3-propenoate was added dropwise. The mixture was allowed to warm up to room temperature over 4 hours, and then quenched with HCl 10%. After the usual workup, mixed epoxyesters were obtained and purified by chromatography on silica gel (hexane/ether/AcOH 3:1:0.5%). Transesterification follows to give the pure ester.

23. The structural data on the epoxides **3** and **4** were collected by ^{1}H (internal reference TMS, 200 MHz), ^{13}C (internal reference TMS, 50 MHz) and ^{19}F (internal reference $CFCl_3$, 188 MHz) NMR, all samples in $CDCl_3$.

3. ^{1}H NMR : 1.25 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3); 3.56-3.67 (m, 1H, $^3J_{HH}$ = 4.2 Hz, $^3J_{HF}$ = 9 Hz, CF_2-CH); 3.67-3.71 (m, 1H, CH-CO); 4.24 (q, 2H, $^3J_{HH}$ = 7 Hz, CH_2). ^{13}C NMR : 13.74 (CH_3); 52.14 (dd, $^2J_{CF}$ = 25.8 Hz, $^2J_{CF}$ = 31.1 Hz, CF_2-CH); 51.45 (d, $^3J_{CF}$ = 3.4 Hz, CH-CO) ; 164.7 (CO). ^{19}F NMR **3a** : -81.3 (CF_3); -121.0 ($CF_2\alpha$); -123.3 ($CF_2\beta$); -124.1 (CF_2); -126.0 ($CF_2\omega$). ^{19}F NMR **3b** : -81.3 (CF_3); -120.4/-121.2/-122.4/ -123.4 (AB syst, $CF_2\alpha$); -123.3 ($CF_2\beta$+γ); -123.3/-123.3 (2 CF_2); -126.7 ($CF_2\omega$).

4. ^{1}H NMR : 1.32 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3); 3.71 (d, 1H, $^3J_{HH}$ = 1.4 Hz, CH-CO); 3.77 (broad t, 1H, CH-CF_2); 4.28 (q, 2H, $^3J_{HH}$ = 7 Hz, CH_2). ^{13}C NMR : 13.86 (CH_3); 48.73 (CH-CO); 52.07 (t, $^2J_{CF}$ = 27.6 Hz, CF_2-CH); 62.65 (CH_2); 165.88 (CO). ^{19}F NMR **4a** : -81.6 (CF_3); -121.6 ($CF_2\alpha$); -122.6 ($CF_2\beta$); -124.2 ($CF_2\gamma$); -126.0 ($CF_2\omega$). ^{19}F NMR **4b** : -81.6 (CF_3); -122.6 ($CF_2\alpha$ + $CF_2\beta$); -123.4/ -123.9 /-124.2 (3 CF_2); -126.9 ($CF_2\omega$).

(Received in France 14 January 1993; accepted 10 February 1993)