Tetrahedron Vol. 42, No. 13, pp. 3623 to 3629, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00
Pergamon Journals Ltd.

SYNTHESIS OF A FLUORINATED ANALOG OF THE SEX PHEROMONE OF THE PROCESSIONARY MOTH *Thaumetopoea pityocampa* (DENIS AND SCHIFF.)[1]

FRANCISCO CAMPS, GEMMA FABRIAS and ANGEL GUERRERO

Departamento de Química Orgánica Biológica (C.S.I.C.),
Jorge Girona Salgado, 18-26
08034-Barcelona. Spain

(*Received in UK* 17 *February* 1986)

Abstract. The synthesis of (E)-13-fluorohexadec-13-en-11-ynyl acetate 1, a fluorinated analog of the sex pheromone of the processionary moth *Thaumetopoea pityocampa* is described. The synthetic scheme involves epoxidation of the double bond, regioselective opening of the oxirane ring with Olah's reagent, tosylation of the resulting fluorohydrin and dehydrotosylation. Structural features of the intermediate diastereomeric fluorohydrins 4a and 4b and tosylates 5a and 5b are also discussed on the basis of their ^{1}H and ^{19}F NMR spectra.

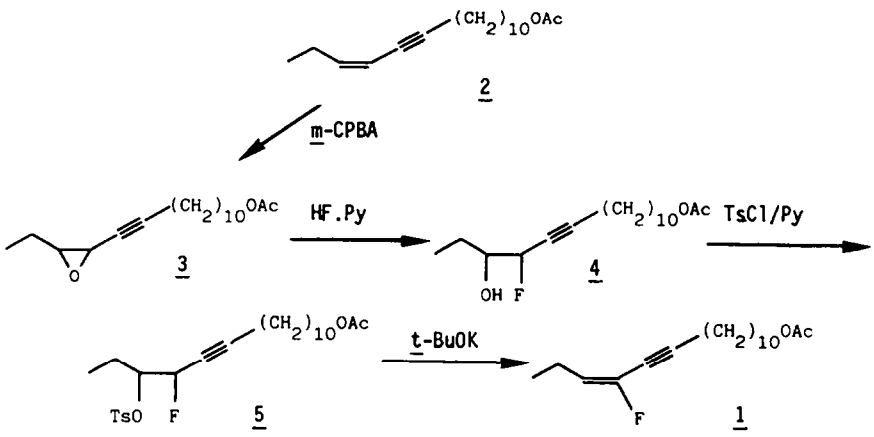
In the last years it has been well established that replacement of hydrogen atoms by fluorine in biologically active compounds results in a variety of effects. Thus, whereas some fluorinated analogs may inhibit or mimic the activity of their parent compounds,[2a-d] other, like fluoroprostaglandins, exhibit an increased biological potency when compared with their non-fluorinated counterparts.[3] In this context, we have recently described the synthesis of several dienic fluorinated analogs of insect sex pheromones,[4,5] that could be expected to act as antipheromones by interfering with the perception process of the natural pheromone. Likewise, Carvalho and Prestwich[6] have shown in bait-block studies that ω-fluoroalcohols, structural analogs of the trail pheromone of the eastern subterranean termite *Reticulitermes flavipes*, may also function as delayed-action toxicants by **in situ** formation of fluoroacetic acid.

In the present communication, continuing our efforts in this field, we report the synthesis of (E)-13-fluoro hexadec-13-en-11-ynyl acetate 1, a fluorinated mimic of the sex pheromone of the processionary moth *Thaumetopoea pityocampa* (Denis and Schiff.) (Lepidoptera, Notodontidae),[7] in which a vinyl hydrogen has been replaced by a fluorine atom.

As shown in Scheme 1, the synthesis of fluoroenyne 1 was accomplished by incorporation of fluorine into the structure of **pityolure** 2, via a four-step sequence, consisting in epoxidation of the double bond and regioselective opening of the oxirane ring with pyridinium poly(hydrogen fluoride) (Olah's reagent),[8] followed by tosylation of the resulting fluorohydrin and dehydrotosylation to regenerate the double bond.

Epoxidation of (Z)-13-hexadecen-11-ynyl acetate[9a-d] 2 with m-CPBA occurred stereospecifically to yield the corresponding epoxyacetate 3 in 81% yield. Although we have not found any precedent in the literature of the reaction of an α,β-acetylenic epoxide with Olah's reagent, it was anticipated that regioselective attack of fluoride ion on C-13 of compound 3 might take place.

Since the triple bond was susceptible to attack by the pyridine-hydrogen fluoride solution,[8] a careful study had to be carried out to find the best experimental conditions for this reaction



Scheme 1

(Table 1). As shown in entry 2, when the reaction was performed at -78° for 30 min, a moderate yield (43%) of fluorohydrin 4 was obtained. Unreacted epoxide 3 (10%), which could be recycled, was also isolated.

Table 1. Ring opening trials of epoxyacetate 3 with Olah's reagent.[a]

Entry	Molar ratio	Temp (°C)	Time (h)	Products (% yield)[b]
1	1	55 to 0	1	4 (15)[c]
2	1	-78	0.5	4 (43) 3 (10)
3	1	-50	0.3	4 (35) 3 (32)
4	1	20	24	Complex mixt.[d]
5	1[e]	20	2	4 (15)
6	1	60	8	4 (22)
7	2	60	3	4 (13)

[a] 70% w/w in HF.

[b] After separation on column chromatography over neutral alumina.

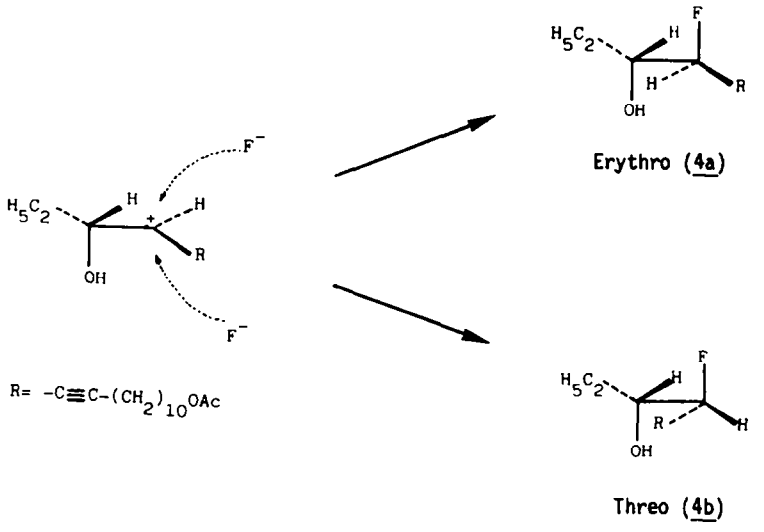
[c] In all cases compound 4 was obtained as a mixture of **erythro** and **threo** diastereomers in a 1:1 ratio.

[d] The corresponding alkyl fluoride from addition of HF to the triple bond could be identified among other products.

[e] HF.Py 40% w/w in HF was used in this case.

Analysis of the reaction products revealed the regioselective formation of fluorohydrin 4, resulting from the attack of the fluoride ion on the most stable intermediate carbenium ion at C-13 (Scheme 2). Unfortunately, the reaction did not occur stereoselectively and a 1:1 mixture of **erythro** and **threo** fluorohydrins was obtained in all cases.[10]

Structural elucidation and conformational analysis of both diastereomers was accomplished by ^{1}H and ^{19}F NMR spectroscopy. Thus, in the ^{1}H NMR spectrum (Figure 1), H-13 of the **erythro** diastereomer 4a appeared as a double doublet of triplets centered at δ 4.96, with coupling constants $J_{H\text{-}13,F}$=49.0 Hz, $J_{H\text{-}13,H\text{-}14}$=4.08 Hz and $J_{H\text{-}13,H\text{-}10}$ =2.0 Hz. Newman projections showed that the most stable fluorohydrin conformers should be those in which the fluorine atom and the hy-



Scheme 2

droxyl group are in **gauche** position (4aI and 4aII) to form an intramolecular hydrogen bond.[11] In both conformations the dihedral angle between H-C(13) and H-C(14) bonds is 60°, which explains the coupling constant magnitude observed for these protons.[12] On the other hand, in **threo** diastereomer 4b the absorption attributable to H-13 appeared as a double doublet of triplets, centered at δ 4.88 with coupling constants $J_{H-13,F}$=49.5 Hz, $J_{H-13,H-14}$=6.6 Hz, and $J_{H-13,H-10}$=2.0 Hz. as part A of a ABM_2X system.

Again, the presence of intramolecular hydrogen bond interactions in the Newman projections of conformers 4bI and 4bII can justify the 2.5 Hz increase of the above coupling constant in comparison with that of the **erythro** compound 4a, due to the important contribution of 4bII (θ=180°) in this case.

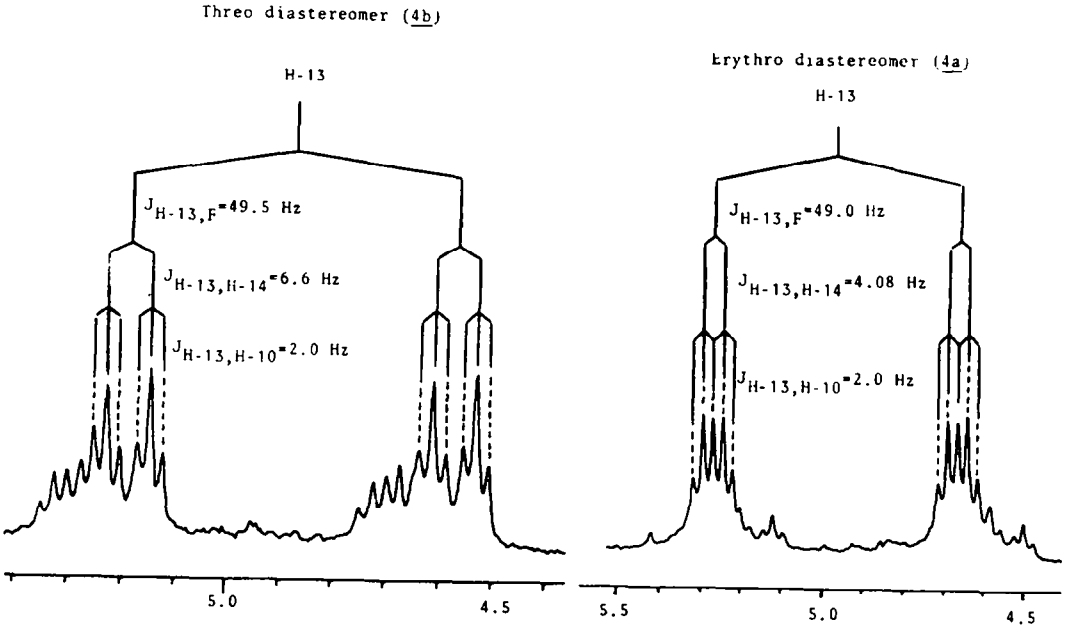


Figure 1

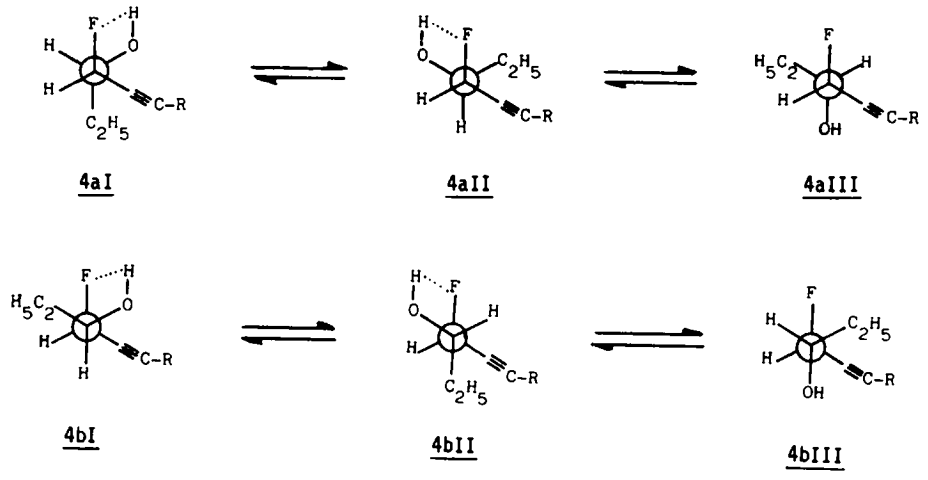


Figure 2

The ^{19}F NMR absorption of 4a and 4b, at δ 104.19 and 104.55 ppm, respectively, corresponded to the expected ABM_2X type with coupling constants $J_{H-13,F} \cong 49$ Hz, $J_{H-14,F} \cong 14$ Hz and $J_{H-10,F} \cong 7$ Hz. The chemical shift difference between both diastereomers was almost negligible ($\Delta\delta = 0.36$ ppm) and this fact can be easily explained by the magnetic equivalence of the fluorine atoms in the preferred conformers of 4a and 4b (see Figure 2).

As shown in Scheme 1, the next step of the above synthetic sequence, required dehydration of the **erythro** diastereomer 4a via the corresponding tosyl derivative 5a. However, the effective separation of both diastereomers by different techniques was unsuccessful (prep. TLC, $AgNO_3$ column chromatography) although a small amount of each diastereomer could be obtained in an isomerically pure state. Tosylation of a 2:1 diastereomeric mixture of 4a:5a, under conventional conditions, yielded the corresponding tosyl derivative 5 in 83% yield.

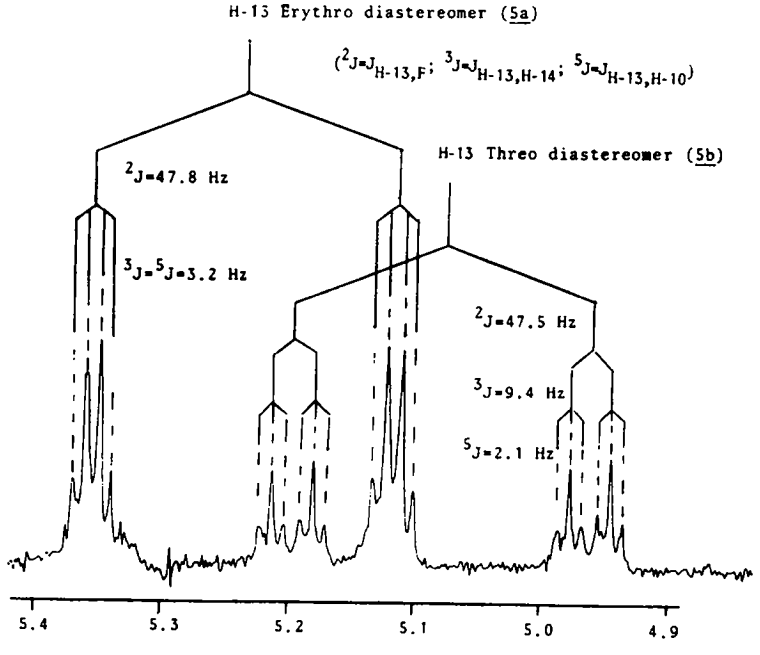


Figure 3

The absorption of the H-13 in the ^1H NMR spectrum of the diastereomeric mixture of tosylates 5a and 5b exhibited a noticeable multiplicity change when compared with that of the starting

fluorohydrins. In fact, as shown in Table 2, the $J_{H-13,H-14}$ in **threo** fluorohydrin 4b was increased 2.8 Hz after tosylation, whereas in the **erythro** diastereomer 4a there was only a slight variation (0.88 Hz). Again, a careful examination of the Newman projections of 5a and 5b provided a plausible explanation for this observation (Figure 4).

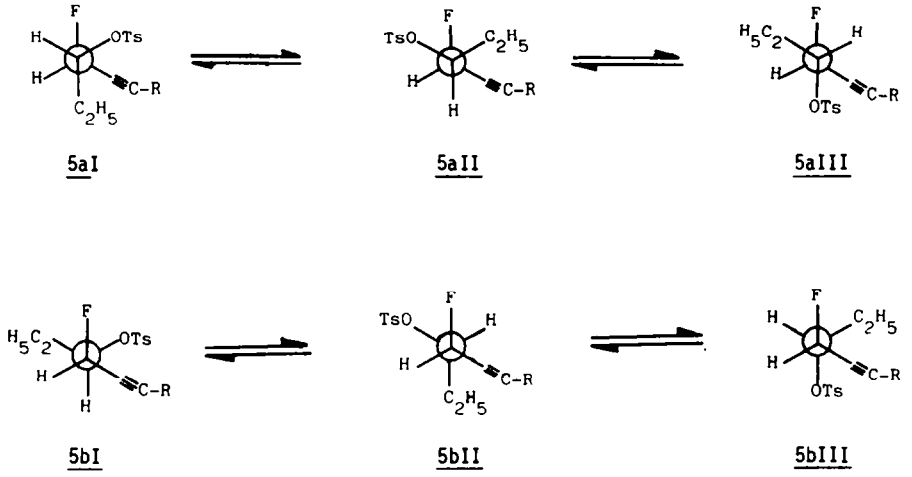


Figure 4

In the **threo** compound 5b the lack of intramolecular hydrogen bond makes 5bII, with the bulkiest groups (OTs and RC≡C) in **antiperiplanar** position, the most preferred conformer. Therefore, the major contribution to the conformational equilibrium of 5bII, in which the dihedral angle of H-13 and H-14 is 180°, causes an increase of the coupling constant value in 5b, in comparison with that observed in 4b, where two different conformations 4bII (θ=180°) and 4bI (θ=60°) were equally probable. Similarly, by the same token, in the **erythro** diastereomer, 5a, the preferred conformation should be 5aII. However, in this case no coupling constant increase should be expected in relation to that of the corresponding fluorohydrin 4a, since in 5aII the dihedral angle of H-13 and H-14 protons (θ=60°) is the same as that of the preferred conformations 4aI and 4aII in compound 4a.

Table 2. ^{19}F NMR and selected ^{1}H NMR spectral data of diastereomers 4a, 4b, 5a and 5b.[a]

	^{1}H NMR			^{19}F NMR
Comp.	δ_{H-13}	J^{b}	ΔJ	δ
4a	4.96	4.08		104.19
			0.88	
5a	5.22	3.2		108.67
4b	4.88	6.6		104.55
			2.8	
5b	5.08	9.4		100.18

[a] δ in ppm relative to TMS and J in Hz.
[b] J H-13, H-14.

On the other hand, whereas a clear separation between both fluorine absorption signals was observed in the ^{19}F NMR spectra of tosylates 5a and 5b, the starting fluorohydrins 4a and 4b exhibited almost identical fluorine chemical shifts (see Table 2). This fact is in agreement with the non-equivalent spatial environments of the fluorine atom in the predominant conformers 5aII and 5bII (Figure 4) in contrast with the similar steric arrangements in the most stable conformers 4aI, 4aII, 4bI and 4bII (Figure 2).

The final step of the above synthetic approach required the dehydrotosylation of compound 5a. However, the attempted separation of the 2:1 diastereomeric mixture of tosylates 5a and 5b was futile. Consequently, the mixture was treated with potassium t-butoxide in DMSO to afford the expected fluoroacetates 1 (E:Z 2:1) in 78% yield (20% overall yield from 2). Assignment of the E configuration to the double bond of the major isomer was done on the basis of the ^1H NMR data. Thus, the vinyl proton appeared as a doublet of triplets centered at δ 5.35 with a $J_{H-14,F}$=15.2 Hz, pointing out a cis H-C=C-F structure (E stereochemistry).[13] On the other hand, the minor isomer displayed the proton absorption at δ 5.01 with $J_{H-14,F}$ =33.7 Hz, clearly indicating a Z stereochemistry of the olefinic bond in this case. Although separation of both isomers by conventional techniques was unsuccessful (prep. TLC and $AgNO_3$ impregnated silica gel), an analytical pure sample of the E isomer was obtained by HPLC.

Preliminary bioassays have shown that compound 1 was slightly active in the field, and when mixed with pityolure 2, in 3:1 or higher ratios, significantly inhibited ($P<0.05$) the action of the synthetic pheromone 2:[14]

EXPERIMENTAL SECTION

Boiling points are uncorrected. Elemental analyses were determined on a Carlo Erba 1106. Infrared spectra were recorded on a Perkin Elmer 399B spectrometer. ^1H NMR spectra were determined in $CDCl_3$ on a Bruker WP80SY (80 MHz) or on a Varian XL200 (200 MHz) spectrometers. ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker WP 80SY operating at 20.15 and 75.39 MHz, respectively. Chemical shifts in ^1H and ^{13}C spectra are reported in δ scale (ppm) relative to TMS, whereas trifluoroacetic acid was used as external standard in the ^{19}F spectra. Gas chromatographic (GLC) analyses were performed on Carlo Erba models 2350 and 4130, equipped with FID detectors, using a 3% OV-101 glass column 2m x 1/8" i.d. on Chromosorb W (nitrogen as carrier gas) or a fused silica capillary column SE-54 50m x 0.32 mm i.d. (hydrogen as carrier gas). HPLC analyses were carried out on a Waters chromatograph employing a Spherisorb ODS-2 column 15 x 0.4cm i.d.

(Z)-13,14-Epoxyhexadec-11-ynyl acetate 3.

To a solution of 5.0 g (18.3 mmole) of (Z)-13-hexadecen-11-ynyl acetate 2 in 60 ml of methylene chloride was added 6.5 g (32 mmole) of m-chloroperbenzoic acid (m-CPBA). After stirring for 6 h at room temperature, 3.71 g (64 mmole) of potassium fluoride, previously dried at 120°C/0.1 Torr for 60 min, was added. The mixture was stirred during 30 min, filtered and the solvent evaporated to give 4.7 g of crude epoxide 3. Purification by column chromatography through neutral alumina (activity III) using hexane:ethyl acetate 95:5 as eluant, yielded 4.4 g (81%) of pure epoxyacetate 3. GLC analysis on capillary column (SE-54) revealed an isomeric purity over 99.5%. IR (CCl_4) ν 2920, 2845, 1740, 1240 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.06 (t J=7.2 Hz, 3H, CH_3CH_2), 1.61 (b, 18H, $CH_2CH_2CH_2$ and CH_2CH_3), 2.03 (s, 3H, CH_3CO), 2.21 (c, 2H, $CH_2C\equiv C$), 2.94 (dt J=6.1 and 4.1 Hz, 1H, CH_2CHO), 3.40 (dt J=4.1 and 1.8 Hz, 1H, $CHOC\equiv$) 4.05 (t J=7.3 Hz, 2H, CH_2OAc). ^{13}C NMR ($CDCl_3$) 64.3 (C-1), 28.3-29.2 (C-2 and C-4 to C-9), 25.7 (C-3), 18.5 (C-10), 75.0 (C-11), 86.0 (C-12), 45.2 (C-13), 58.8 (C-14), 22.5 (C-15), 9.6 (C-16), 20.6 (C-1'), 170.7 (CO). Anal. Calcd. for $C_{18}H_{30}O_3$: C, 65.98; H, 10.20. Found: C, 65.70; H, 9.92.

13-Fluoro-14-hydroxyhexadec-11-ynyl acetate 4.

A solution of 4.2 g (14.28 mmole) of epoxyacetate 3 in 20 ml of methylene chloride was quickly added to 15 ml of 70% HF-pyridine complex, previously cooled to -78°C. The resulting solution was stirred at this temperature for 45 min, poured into ice-water and extracted with methylene chloride (5 x 50 ml). The combined organic extracts were washed with 5% $NaHCO_3$ solution and water and dried ($MgSO_4$). The solvent was stripped off leaving an oily residue (4.64 g), which was purified by column chromatography on neutral alumina (act. III). By using hexane:ethyl acetate 90:10 as eluant 0.43 g (10%) of epoxyacetate 3 was recovered unchanged, whereas elution with the same mixture in 85:15 ratio afforded 1.91 g (43%) of the expected erythro and threo fluorohydrins 4 in a 1:1 ratio. Separation of both diastereomers by flash chromatography on silica gel was only partially successful. Thus, starting from 0.68 g of the diastereomeric mixture and using hexane:ethyl acetate 85:15 as eluant, were obtained 0.13 g of pure threo diastereomer 4b, 0.48 g of mixture of several

ratios and 0.16 g of pure **erythro** 4a. IR (CCl_4) ν 3600, 3350, 2930, 2850, 2230, 1745, 1250, 1215 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00 (t J=7 Hz, 3H, CH_3CH_2), 1.30 (b, 18H, $CH_2CH_2CH_2$ and CH_2CH_3), 2.0 (s, 3H, CH_3CO), 2.22 (c, 2H, $CH_2C{\equiv}C$), 3.64 (c, 1H, CHOH), 4.05 (t J=6.2 Hz, 2H, CH_2OAc), 4.88 (ddt J=49.5, 6.6 and 2.0 Hz, 1H, CHF of the **threo** diastereomer), 4.96 (ddt J=49.0, 4.08 and 2.0 Hz, 1H, CHF of the **erythro** diastereomer). ^{19}F NMR **Erythro** diastereomer: 104.19 (ddt J=49.0, 14.5 and 7.0 Hz), **threo** diastereomer: 104.55 (ddt J=49.1, 13.9 and 7.2 Hz). Trials to prepare 4 under other experimental conditions furnished the fluorohydrin in lower yields (Table 1).

13-Fluoro-14-tosylhexadec-11-ynyl acetate 5.

A mixture of 0.6 g (3 mmole) of tosyl chloride, 0.21 g (10.6 mmole) of a diastereomeric mixture **erythro**:**threo** 2:1 of fluorohydrins 4 and 2.4 ml of anhydrous pyridine was stirred at room temperature for 15 h. After pouring into 10 ml of water and extraction with ether (6 x 25 ml), the extracts were washed successively with 2N HCl, $NaHCO_3$ saturated solution and brine and dried. Removal of solvent afforded 0.26 g (83%) of crude tosylate 5, pure enough, according to the expected spectroscopic data, to be used for the next step without further purification. IR (CCl_4) ν 2940, 2850, 2230, 1750, 1595, 1365, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (t J=7.1 Hz, 3H, CH_3CH_2), 1.34 (b, 16H, $CH_2CH_2CH_2$) 1.85 (c, 2H, CH_2CH_3), 2.05 (s, 3H, CH_3CO), 2.21 (c, 2H, $CH_2C{\equiv}C$), 2.46 (s, 3H, $ArCH_3$), 4.05 (t J=6.8 Hz, 2H, CH_2OAc), 4.57 (c, 1H, CHOTs), 5.08 (ddt J=47.5, 9.4 and 2.1 Hz, 1H, CHF of the **threo** diastereomer), 5.22 (dq J=47.8 and 3.2 Hz, 1H, CHF of the **erythro** diastereomer). ^{19}F NMR **Erythro** diastereomer: 108.67 (c), **threo** diastereomer: 100.18 (c).

(E)-13-Fluorohexadec-13-en-11-ynyl acetate 1.

A solution of 0.28 g (0.42 mmole) of a diastereomeric mixture of tosylates 5a:5b 2:1 in 2.3 ml of anhydrous benzene was added to a vigorously stirred mixture of 83 mg (0.63 mmole) of t-BuOK and 2.3 ml of anh. DMSO. The reaction mixture was stirred for 14 h at room temperature, poured into ice-water and extracted with hexane (5 x 10 ml). The combined organic solutions were washed successively with 2N HCl, $NaHCO_3$ sat. sol. and brine and dried ($MgSO_4$). The solvent was evaporated under vacuum to yield 0.12 g of crude fluoroacetate 1, which was chromatographed on silica gel. Elution with hexane:ethyl acetate 97:3 gave 97 mg (78%) of pure compound 1 as a 2:1 E:Z isomer mixture, according to GLC analysis on a SE-54 fused silica capillary column. Trials to separate both stereoisomers on TLC or $AgNO_3$ impregnated silica gel were unsuccessful but the required isomer E-1 could be isolated on HPLC. ^1H NMR ($CDCl_3$) of E-1: δ 0.98 (t J=7.2, 3H, CH_3CH_2), 1.27 (c, 16H, $CH_2CH_2CH_2$), 2.02 (s, 3H, CH_3CO), 2.15 (c, 4H, $CH_2C{=}C$ and $CH_2C{\equiv}C$), 4.01 (t J=6.5 Hz, 2H, CH_2O), 5.35 (dt J=15.2 and 7.1 Hz, 1H, CH=C). Z-1: δ 5.01 (dt J=33.7 and 7.1 Hz, 1H, CH=C). ^{13}C NMR of E-1: 64.9 (C-1), 28.1-29.3 (C-2 and C-4 to C-9), 25.8 (C-3), 19.1 (C-10), 78.1 (C-11), 98.5 (C-12), 142.7 (C-13), 117.7 (C-14), 17.8 (C-15), 13.4 (C-16), 20.9 (C-1'), 170.9 (CO). ^{19}F NMR of E-1: 30.6 (c); Z-1: 32.7 (c).

Acknowledgements. The authors wish to thank the CAICYT for financial support (Grant N° 263-85) and Consejo Superior de Investigaciones Científicas for a predoctoral fellowship to one of us (G.F.).

REFERENCES and NOTES

1. Taken in part from G. Fabriàs, Ph.D. Thesis. Universidad de Barcelona, 1985.
2a. M. Schlosser, Tetrahedron Report No. 31, 1-15 (1977).
2b. T.B. Patrick, J. Chem. Ed. 56, 228 (1979).
2c. R. Filler, Chem. Tech. 4, 752 (1974).
2d. J.A. Pickett, private communication.
3. P.A. Grieco, T. Takigawa and T.R. Vedananda, J. Org. Chem. 50, 3111 (1985).
4. F. Camps, J. Coll, G. Fabriàs, A. Guerrero and M. Riba, Experientia 40, 933 (1984).
5. F. Camps, J. Coll, G. Fabriàs and A. Guerrero, Tetrahedron 40 (15), 2871 (1984).
6. J.F. Carvalho and G.D. Prestwich, J. Org. Chem. 49, 1251 (1984).
7. A. Guerrero, F. Camps, J. Coll, M. Riba, J. Einhorn, Ch. Descoins and J.Y. Lallemand, Tetrahedron Lett. 22 (21), 2013 (1981).
8. G.A. Olah, J.T. Welch, Y.D. Vankar, M. Nojima, I. Kerekes and J.A. Olah, J. Org. Chem. 44, 3872 (1979).
9a. F. Camps, J. Coll, R. Canela, A. Guerrero and M. Riba, Chem. Lett. 703 (1981).
9b. D. Michelot, A. Guerrero and V. Ratovelomanana, J. Chem. Res. (S) 93 (1982).
9c. A. Shani, J.T. Klug and J. Skorka, J. Chem. Ecol. 9 (7), 863 (1983).
9d F. Camps, J. Coll, A. Guerrero and M. Riba, J. Chem. Ecol. 9 (7), 869 (1983).
10. The reaction has been described to be stereoselective for α,β-epoxyesters. See, for instance, A.I. Ayi, M. Remli, R. Condom and R. Guedj, J. Fluorine Chem. 17, 565 (1981) and J. Julien, J.A. Martin and R. Ramanadin, Bull. Soc. Chim. France 171 (1964).
11. Several fluorinated compounds have been described to exist almost entirely in the gauche form. See W. Jones and O. Thomas, J. Mol. Struct. 1, 79 (1967) and N. Hagen and K. Hedberg, J. Am. Chem. Soc. 95, 8263 (1973).
12. M. Karplus, J. Chem. Phys. 30, 11 (1959).
13a. M. Hudlicky, Chemistry of Organic Fluorine Compounds, p. 577. Ellis Horwood Ltd (1976).
13b. C.H. Dungan and J.R. Van Wazer, Compilation of reported ^{19}F NMR chemical shifts. Wiley Interscience, New York, N.Y. (1970).
14. Field test activity results will be published in due course.