Tetrahedron Vol. 44, No. 16, pp. 5161 to 5167, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

ON THE COHERENCE OF INCORPORATION OF THE FLUOROVINYL MOIETY INTO BIOACTIVE ORGANIC COMPOUNDS. SYNTHESIS OF AN INSECT JUVENILE HORMONE III FLUORINATED ANALOG.

F. Camps*, A. Messeguer and Francisco-José Sánchez.
Department of Biological Organic Chemistry, C.I.D., (C.S.I.C.)
J. Girona Salgado 18-26. 08034-Barcelona, Spain.

(*Received in UK* 16 *May* 1988)

ABSTRACT

An insect juvenile hormone fluoroanalog, methyl 10-fluoro-10,11-epoxyfarnesoate (9), has been prepared, using tandem Claisen-Cope rearrangements on fluorovinyl intermediate 1 as a crucial step. Along this synthesis chemical and spectral data have been obtained that might question some applications of fluorovinyl derivatives in the design of bioactive organic compounds.

INTRODUCTION

The unique properties of fluorine have been widely used to modify the behavior of bioactive compounds. The electron-withdrawing character of this halogen confers a strong polarization to the carbon site involved, while preserving the topology and lipophilicity of the original molecule. The overall effect frequently results in a deactivation towards detoxifying metabolism[1].

In particular, this strategy has been applied to the case of fluorovinyl compounds. Thus, several reports have been published in which introduction of fluorine into carbon double bonds of bioactive molecules has been carried out with the aim of enhancing the chemical and metabolic stability of this moiety[2-5]. Moreover, results from thermodynamic studies have also led to the conclusion that it should be a net energy stabilization gain in monofluoro and gem-difluoro-ethylenic systems in comparison with their hydrogen counterparts[6].

With these antecedents in mind, and pursuing our interest in the study of organic fluorinated compounds as analogs[7] and antagonists[8] of insect juvenile hormones, we contemplated the introduction of fluorine atoms in the vicinity of the terminal double bond of methyl farnesoate, the intermediate which is epoxidized by a P-450 system in the final biosynthetic step leading to juvenile hormone III in several insect orders[9].

In the present paper, we report on the synthesis of compound 8, a fluoroanalog of methyl farnesoate bearing the halogen atom on the terminal double bond of the sesquiterpene chain. Likewise, assays on the epoxidation of 8, as well as selected spectroscopic features of different synthetic intermediates, which might question the putative deactivation effect of fluorovinyl moiety, are also discussed.

RESULTS AND DISCUSSION

The synthetic sequence used for the preparation of fluoroepoxide 9 is depicted in the Scheme. A priori, from other syntheses of JH III analogs carried out in our laboratory[10,11], two crucial steps might be anticipated in this case, i.e., the tandem Claisen-Cope rearrangements designed to convert ester 1 into the monoterpene intermediate 4, and the final regioselective epoxidation of

the fluorofarnesoate 8. Both processes involved the direct participation of the fluorovinyl moiety and, to our knowledge, there were no precedents in the literature for predicting the course of these reactions.

The use of tandem Claisen-Cope rearrangements for chainlengthening allylic alcohols in an isoprene unit was first described by G. Fráter[12] in the preparation of insect juvenile hormones. However, in the case of JH III, the lack of stereospecificity of Cope rearrangement led to the formation of E/Z isomers both at the inner and conjugated double bonds of the sesquiterpene reaction product. On the other hand, Ireland et al.[13] independently published a detailed study on the stereochemical outcome of the ester enolate Claisen rearrangement.

Concerning to the Claisen and Cope rearrangements carried out with fluorinated compounds, there have been several reports in the literature, although we have not found any example directly related to our case. Thus Yokozawa et al.[14] studied the α-allylation of α,β,β-trifluoropropionic esters via the enolate Claisen rearrangement of 2-alkenyl trifluoropropionates, and more recently, Welch and Samartino[15] reported examples of diastereoselective ester enolate Claisen rearrangements of allyl fluoroacetates. It is worth to point out that in both cases fluorine was linked to a carbon atom of the acyl part of the molecule, and although the formation of the intermediate enolate supposes the conversion of the above sp^3 carbon atom into a sp^2 hybrid, rearrangement restored the original saturated character of that atom. According to the results of Dolbier et al.[6], there is a thermodynamic stabilization of the saturated C-F in front of the vinylic =C-F. This difference might be the driving force that favored the course of the rearrangement. Finally, Metcalf et al.[16] described Claisen rearrangements of compounds containing two fluorine atoms in either the allyl or the vinyl fragments, but again in the final products the fluorine atom was on a saturated carbon atom.

With these antecedents, we carried out a preliminary assay on the ester enolate Claisen rearrangement of ester 1. Reaction took place smoothly and acid 3 was isolated in 75% yield. In this case, both the starting compound and the product contained a vinylic =C-F, which confirmed that even in the absence of the above mentioned driving force, fluorovinyl moieties become stabilized enough to allow these reactions to proceed. Furthermore, when the Cope rearrangement on acid 3 was attempted under moderate thermal conditions (reflux in N,N-dimethylformamide), a 9:1 2E:2Z isomeric mixture (^{19}F NMR) of acid 4 was isolated in 74% yield. Again, a smooth rearrangement from a fluorovinyl moiety into another had taken place. Finally, when we carried out the above combined Claisen-Cope processes on fluoroester 1, in a one pot reaction, a 70% overall yield of 4 was obtained. Separation of isomers was accomplished by flash chromatography of the corresponding methyl esters.

The above mentioned works of Fráter[12] and Ireland et al.[13] on the stereochemical course of the Claisen and Cope rearrangements, discouraged us from using a second tandem transformation for lengthening the monoterpene intermediate 5 in one isoprene unit. As alternative, we turned to the synthetic approach reported by Liedke and Djerassi[17] , with some improvements, which basically involved an initial acetoacetic condensation on the bromoderivate 6 to give fluorinated ketone 7. Subsequent Horner-Emmons olefination afforded fluoroester 8 as a 2E:2Z 74:26 mixture (GLC), which was separated by preparative TLC.

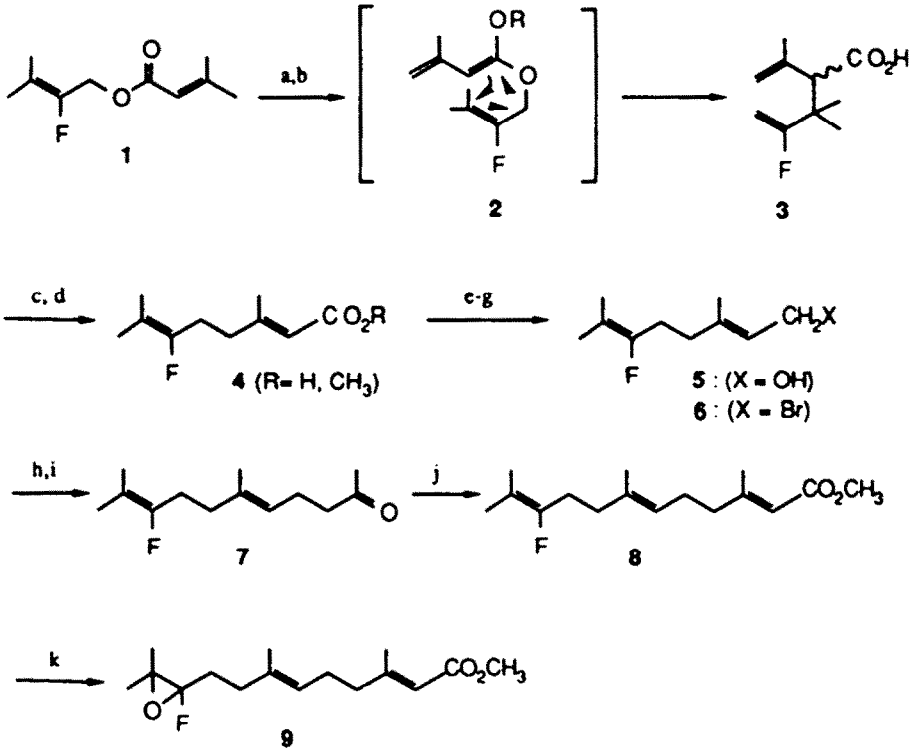
The other synthetic step which could be influenced by the presence of fluorine was the regioselective conversion of fluorofarnesoate 8 into the epoxide 9. Literature about fluoroepoxides is scarce, although Atlani and Leroy[18] reported the preparation of monofluoroepoxides via the dehydrohalogenation of halohydrins and they found that these fluorinated epoxides were thermally unstable. More recently, Leroy reported the m-chloroperoxybenzoic acid epoxidation of several 1,2-difluoroethylenic compounds. The corresponding epoxides were isolated in good yields with the exception of that coming from a styrene derivate, which was not even detected[19] . On the other hand, we have recently observed that epoxidation of double bonds bearing trifluoromethyl groups did not occur under conventional peroxyacid treatment[11].

With these antecedents, a preliminary assay on the epoxidation of fluoroester 4 with m-chloroperoxybenzoic acid in deuterochloroform solution was attempted. Monitoring the reaction

course by NMR, at the temperature of the probe (32°C), showed that conversion was rapid and clean to afford the expected fluoroepoxide in nearly quantitative yield. Identification of this compound was carried out by spectral means. Thus, fluorine absorption in the ^{19}F NMR spectrum appeared as a triplet at -60.5 pm (J=18 Hz), which was approximately -23 ppm shifted in comparison with that of the precursor fluoroolefin, suggesting an important enhancement of electron density in the vicinity of fluorine, as expected from the presence of an oxiran ring. Additionally, the shift of the terminal methyl groups absorptions (1.44 and 1.29 ppm), when compared to those of fluoroester 4 (1.64-1.56 ppm) in the ^{1}H NMR spectrum, confirmed the assignation.

This result, which indicated that a monofluorinated double bond similar to that occurring in fluorofarnesoate 8 was not deactivated towards peroxyacid epoxidation, was encouraging enough to assay the epoxidation on this substrate, in which a previsible competition between fluorinated and non-fluorinated double bonds could take place. Accordingly, as shown in Table 1, epoxidation of 8 was carried out at different temperatures and parallel control experiments were also performed with methyl farnesoate under the same conditions for comparison purposes.

SCHEME



(a) LDA/THF/-75°C; (b) $(CH_3)_3SiCl$/-75° to 25°C/ 1 h; (c) DMF/ 150°C/1 h (9:1 2E:2Z, 78% overall a-c); (d) CH_3I/K_2CO_3/acetone/25°C/24 h (82% in 2E isomer); (e) LAH/ether/-20° C/1 h (94%); (f) $(CF_3CO)_2O$/ pyridine/THF/-20°C/15 min; (g) LiBr/THF/HMPA/-20°C/1 h (85% overall f-g). (h) $K^tBuO/CH_3COCH_2CO_2C_2H_5$/dioxane/25°C/18 h; (i) DMSO/H_2O/NaCl/ 170°C/3 h (80% overall h-i); (j) NaH/$(CH_3O)_2P(O)CH_2CO_2CH_3$/benzene/ 60°C/12 h (74% in 2E isomer); (k) mCPBA/CH_2Cl_2/45°C/1 h (30%).

Thus, in the reaction with ester 8, low temperatures favored the regioselective epoxidation of the non-fluorinated, inner double bond. This is in contrast with the results obtained with methyl farnesoate, in which it is known that steric factors determine higher epoxidation rates at the terminal double bond. Therefore, it seems that fluorine does induce some sort of deactivation towards electrophilic attack on the olefin. At higher reaction temperatures, conversion of 8 was faster and the formation of fluoroester 9 was rapidly increasing until a 1:1 epoxides ratio was attained by performing the oxidation at 45°C.

Table 1: Assays on the epoxidation of methyl farnesoate (MF) and methyl 10-fluorofarnesoate (8) with an equimolecular amount of m-chloroperoxybenzoic acid in dichloromethane, at different temperatures[a].

T(°C)	8			MF			
	8[b,c]	9[c]	6,7-epoxide[c]	MF[b,d]	10,11-epoxide[d]	6,7-epoxide[d]	diepoxide[d]
-20	30	0	70	14	57	9	19
0	20	20	60	-	-	-	-
20	30	25	45	-	-	-	-
45	20	40	40	28	32	19	26

a For more details, see Experimental.
b Percentage of unreacted starting compound.
c Percentage estimated by ^{19}F NMR.
d Percentage estimated by GLC.

Another feature from this study was that related to the formation of a diepoxide. It is also known that peroxyacid epoxidation of methyl farnesoate gives an important amount of the corresponding diepoxide (see Table 1), which mostly comes from further oxidation of the 6,7-epoxyderivative. However, in the case of fluoroester 8, we were not able to detect the formation of the corresponding diepoxyderivative under the reaction conditions used. This fact could also be rationalized as consequence of the deactivation induced by fluorine on the double bond. Thus, these data indicate that fluorovinyl moieties are less reactive than their hydrogen counterparts towards peroxyacid epoxidation, although the effect does not appear to be so strong as it occurs in systems like those in which a trifluoromethyl or a carbonyl group are linked to the double bond.

In another context, IR and ^{13}C NMR spectral data of fluorovinyl compounds also deserve some comments. Concerning to the IR of fluorovinyl compounds[20], intermediates without carbonyl groups, such as alcohol 5 and bromoderivative 6, showed a misleading absorption at 1720 cm^{-1}, which should be assigned to the stretching vibration of the fluorinated double bond. The high frequency of this absorption suggests that the net result of fluorine influence on the olefinic moiety could be an enhancement of the bond order, probably through a backdonation effect from the p electrons of this halogen atom.

Likewise, ^{13}C NMR absorptions of fluorovinyl carbon atoms reported in the literature[21] and those from our present study support the hypothesis that fluorine exerts that backdonation along with the electron-withdrawing inductive effect. Thus, as an example in fluoroester 8, the absorption assigned to C-10, the carbon atom supporting the fluorine, occurs at 154 ppm. This value is shifted only 19 ppm when compared with the absorption of a quaternary carbon atom such as C-7 (135 ppm). This shift is much smaller than that observed in the corresponding replacement of a carbon by a fluorine at saturated carbon atoms (approximately 60 ppm[22]), indicating that some counterbalance to the purely inductive effect of the fluorine should occur at the C-F bond of fluorovinyl derivatives. In addition, the comparison of the corresponding C-11 absorptions in

fluoroester 8 and methyl farnesoate[23] (107 and 131 ppm, respectively) seems to confirm the above hypothesis. In fluoroester 8, C-11, the olefinic carbon atom not directly linked to fluorine is shielded indicating a net electron density gain on its environment.

In summary, a straightforward preparation of JH III fluoroanalog 9 has been carried out involving tandem Claisen-Cope rearrangements on fluorovinyl intermediate 1 as a crucial step. The whole sequence comprised ten steps and epoxide 9 was isolated in 9% overall yield. On the other hand, chemical and spectral characteristics of the fluorovinyl group have been obtained along this synthesis that might question some applications of this moiety in the design of bioactive organic compounds. Our data indicate a dual opposite effect of fluorine atom on the double bond carbon atoms of the fluorovinyl group: an inductive electron-withdrawing effect that acts mainly on the carbon atom directly linked to the halogen, counterbalanced by a backdonation from the fluorine atom to the π olefin electronic system. As a net result, the double bond is much less deactivated that might be a priori expected. Consequently, the fluorovinyl derivatives should be not much more stable than their corresponding hydrogen counterparts against environmental and metabolic degradations.

Preliminary results on the biological activity of the compound 8 as a potential JH biosynthesis inhibitor and some observations from this laboratory on the chemistry and activities of fluorinated analogs of insect sex pheromones seem to agree with the above statements. Further confirmation of this dual effect by theoretical calculations is now in progress and will be reported elsewhere in due time.

EXPERIMENTAL SECTION

IR spectra were run in carbon tetrachloride solutions on a Perkin Elmer 399 B instrument. NMR spectra were recorded in deuterochloroform solutions (unless otherwise stated) on a Bruker WP-80 SY apparatus operating at 80.13 MHz for ^{1}H, 20.15 MHz for ^{13}C and 75.39 MHz for ^{19}F. The fluorine chemical shifts are reported in δ ppm units using a 1% solution of trifluoroacetic acid in deuterochloroform as external standard. GC/MS analyses with electron impact were performed with a Hewlett-Packard model 5995-C instrument, using a OV-101 glass capillary column (25 m). Microanalyses were performed with a Carlo Erba model 1106 instrument.

2-Fluoro-3-methylbut-2-enyl 3-methylbut-2-enoate (1):
A mixture of 3-methyl-2-butenoic acid (17.8 g, 0.18 mol), 2-fluoro-3-methylbut-2-enol[24] (14.8 g, 0.14 mol), N,N'-dicyclohexylcarbodiimide (39.2 g, 0.19 mol) and N,N-dimethylaminopyridine (1.71 g, 0.014 mol) in dichloromethane (350 ml) was stirred for 24 h at 25°C. Then formic acid (5 ml) was added and the crude reaction mixture was stirred for 5 min and filtered through Celite. The residue obtained after solvent elimination was purified by flash chromatography (9:1 hexane:ether), to furnish ester 1 as a colorless oil (22.8 g, 87%). IR: ν = 1740; 1660 cm^{-1}; ^{1}H NMR: δ = 5.80(br s,1H); 4.70(d,2H,J=22Hz); 2.18(d,3H,J=1.5Hz); 1.90(d,3H,J=1Hz); 1.72(s,3H) and 1.70 (s,3H).
Calculated for $C_{10}H_{15}FO_2$: C=64.52;H=8.06. Found: C=64.66;H=8.12.

5-Fluoro-2,4,4-trimethyl-2,5-hexadien-2-carboxylic acid (3):
A solution of ester 1 (1.0 g, 5.4 mmol) in tetrahydrofuran (5 ml) was added dropwise to a 0.5 M solution of lithium diisopropylamide in the same solvent (5.7 ml), maintained at -75°C, and the mixture was stirred for 30 min at that temperature. Then, trimethylsilyl chloride (0.60 g, 5.5 mmol) was added and the reaction mixture was slowly warmed up to room temperature (2 h) and heated under reflux (1 h). After the careful addition of water (1 ml), the crude reaction mixture was poured into 1.5 N sodium hydroxide solution (20 ml) and washed with ether. The aqueous layer was acidified, extracted with ether and the organic extracts were washed with water and dried over magnesium sulphate. The residue obtained after solvent evaporation afforded the acid 3 (0.76 g, 76%), which was characterized as methyl ester (vide infra). ^{1}H NMR: δ = 5.07(2H); 4.68-4.06 (complex,2H); 3.39(s,1H); 1.87(d,3H,J=1Hz); 1.30(s,3H) and 1.26(s,3H). ^{19}F NMR: δ = -27.1(dd, J_1=51, J_2=19 Hz).
A solution of acid 3 (0.186 g, 1 mmol) in acetone (10 ml) was treated with potassium carbonate (1.38 g, 10 mmol) and iodomethane (0.28 g, 2 mmol) and the mixture was stirred for 12 h at room temperature. Then, hexane (20 ml) was added and the crude reaction mixture was filtered. The elimination of solvent afforded the expected methyl ester as a colorless oil (0.190 g, 95%). ^{1}H NMR (C_6D_6): δ= 5.15(br,2H); 4.32(dd,1H,J_1=51,J_2=3Hz); 4.55(dd,1H,J_1=19,J_2=3Hz); 3.63(s,1H); 3.42(s,3H); 1.90(br,3H); 1.38(s,3H); 1.34(s,3H). ^{13}C NMR: δ= 172; 170(d,J=280Hz); 140; 117; 89(d,J=22Hz); 57; 51; 41(d, J=2Hz); 24,23.7(d,J=3Hz); 22.4. MS: m/e= 200(M^+); 180(M^+-HF); 169(M^+-OCH_3).
Calculated for $C_{11}H_{17}FO_2$: C=66.00;H=8.50. Found: C=66.21;H=8.56.

6-Fluoro-3,7-dimethyl-2,6-dienoic acid (4; R=H)
A solution of 3 (0.70 g, 3.8 mmol) in N,N-dimethylformamide (4 ml) was heated under reflux for 1.5

h. The crude reaction mixture was poured into 1 N sodium hydroxide solution (50 ml), washed with ether and the aqueous fraction was acidified and extracted with ether (3x10 ml). The acid organic extracts were washed with water and dried over magnesium sulphate. Removal of solvent under vacuum afforded acid 4 as a 9:1 2E:2Z (^{19}F NMR) isomeric mixture (0.520 g, 74%), which was characterized through the respective methyl esters (vide infra). IR: ν = 3300-2700; 1705; 1640 cm^{-1}. ^{1}H NMR: δ = 5.72 (br,1H); 2.8-2.2(complex,4H); 2.17(d,3H,J=1.5Hz); 1.65-1.60(complex,6H). ^{19}F NMR: δ = -36.5(t,J=13Hz).

One pot transformation of ester 1 into acid 4.
A solution of ester 1 (5.0 g, 27 mmol) in tetrahydrofuran (10 ml) was added dropwise to a 0.5 M solution of LDA in the same solvent (60 ml), maintained at -75°C. The mixture was stirred for 10 min at that temperature and trimethylsilyl chloride (3.2 g, 30 mmol) was added. Then, stirring was continued until the mixture slowly reached room temperature (approx. 1 h) and a distillation system was adapted to the reaction flask. After heating for 1 h at 50°C, N,N-dimethylformamide (40 ml) was added and the mixture was heated up for 1 h at 150°C. Work-up of the crude reaction mixture as described above led to the isolation of acid 4 as a 9:1 2E:2Z (^{19}F NMR) isomeric mixture (3.90 g, 78% overall).

Methyl 6-fluoro-3,7-dimethylocta-2,6-dienoate (4; R=CH$_3$).
Potassium carbonate (46.5 g, 0.34 mol) and iodomethane (36.0 g, 0.25 mol) were added to a solution of acid 4 (15.6 g, 0.084 mol) in acetone (300 ml). The mixture was stirred until reaction was completed (24 h, 25°C). Treatment of the crude reaction mixture as described above for methyl ester 3 led to a residue containing methyl ester 4 (15.9 g, 95%) in the same isomeric ratio as the parent acid. Separation of isomers was accomplished by flash chromatography (95:5 hexane:ether) to give pure ester 2E (13.8 g, 82%) and 2Z (1.51 g, 9%).
2E Isomer IR: ν= 1715; 1645; 1280 cm^{-1}. ^{1}H NMR: δ = 5.69(q,1H,J=1Hz); 3.68(s,3H); 2.6-2.2(complex, 4H); 2.17(d,3H,J=1.5Hz); 1.64-1.56(complex,6H). ^{19}F NMR: δ = -36.5(m,J =15,J =3Hz). ^{13}C NMR: δ = 167; 160; 154 (d,J=242Hz); 124; 107(d,J=18Hz); 50.5; 37.5; 27.5(d,J=30Hz); 18.6; 17.3(d,J=6Hz); 15.3(d,J=9Hz). MS: m/e= 200(M$^+$); 180(M$^+$-HF); 169(M$^+$-OCH$_3$).
Calculated for $C_{11}H_{17}FO_2$: C=66.00;H=8.50. Found: C=65.79;H=8.53.

2Z Isomer IR: ν = 1720; 1645 cm^{-1}. ^{1}H NMR: δ = 5.62(br,1H); 3.65(s,3H); 2.5-1.7(complex,4H); 1.82(s,3H); 1.64-1.56(complex,6H). ^{19}F NMR: δ = -36.0(t,J=15Hz).

(E)-6-Fluoro-3,7-dimethylocta-2,6-dienyl bromide (6).
A solution of ester 4 (4.0 g, 20 mmol) in ether (20 ml) was added dropwise to a suspension of lithium aluminium hydride (0.80 g, 20 mmol) in the same solvent (20 ml), maintained at -20°C, and the mixture was stirred for 30 min at that temperature. After the careful addition of water, the crude reaction mixture was filtered and dried over magnesium sulphate. Elimination of solvent gave the corresponding fluorinated alcohol 5 (3.23 g, 94%, over 98% purity by GLC). IR: ν= 3600-3200; 1720; 1645; 1020 cm^{-1}. ^{1}H NMR: δ = 5.42(t,1H,J=7Hz); 4.15(d,2H,J=7Hz); 2.6-2.0(complex,4H); 1.75(s, 3H); 1.65-1.55(complex,6H). ^{19}F NMR: δ = -36.2(t,J=18Hz). MS: m/e=172(M$^+$); 154(M$^+$-H$_2$O); 152(M$^+$-HF).
Calculated for $C_{10}H_{17}FO$: C=69.77;H=9.88. Found: C=69.52;H=10.01.

Following a method recently developed in our laboratory[25], pyridine (2.37 g, 30 mmol) and trifluoroacetic anhydride (4.62 g, 22 mmol) were added to a solution of fluoroalcohol 5 (3.59 g, 20 mmol) in tetrahydrofuran (25 ml), maintained at -20°C. The mixture was stirred until reaction was complete (15 min), then concentrated to dryness and redissolved in pentane (25 ml). After filtration and evaporation of solvent, the new residue, containing the corresponding trifluoroacetic ester, was dissolved in tetrahydrofuran (10 ml), mixed with lithium bromide (8.7 g, 100 mmol) and cooled down to -20°C. Then hexamethylphosphorous triamide (10 ml) was added and the mixture was stirred for 1 h at the same temperature. The crude reaction mixture was poured into water (200 ml) and extracted with pentane (5x25 ml). The joined organic extracts were washed with water, dried over magnesium sulphate and evaporated under darkness. The residue obtained after solvent removal was identified as the bromoderivative 6 (4.5 g, aprox. 90% purity by GLC). For characterization purposes, an aliquote of this crude was purified by bulb to bulb distillation (95-100°C/10 Torr). ^{1}H NMR: δ = 5.56(br t,1H,J.7Hz); 3.98(d,2H,J=7Hz); 2.6-2.1(complex,4H); 1.78(s, 3H); 1.65-1.55(complex,6H). MS: m/e= 238 and 236(M$^+$); 218 and 216(M$^+$-HF); 157(M$^+$-Br).
Calculated for $C_{10}H_{16}BrF$: C=50.63;H=6.75. Found: C=51.15;H=7.01.

9-Fluoro-6,10-dimethyl-5,9-undecadien-2-one (7).
The bromide 6 (4.22 g, 16 mmol) was added to a mixture of ethyl acetoacetate (5.2 g, 40 mmol) and potassium tert-butoxide (3.6 g, 32 mmol) in dioxane (100 ml) previously stirred at room temperature for 1 h. After stirring for 18 h at the same temperature, the crude reaction mixture was neutralized with ammonium chloride (2 g), poured into water (750 ml) and extracted with ether (5x100 ml). The organic extracts were washed with water and dried over magnesium sulphate. The residue obtained after elimination of solvents under vacuum (5.6 g) was redissolved in dimethylsulfoxide (50 ml) and mixed with a solution of sodium chloride (3 g) in water (4 ml). The mixture was heated at 170°C until no more carbon dioxide was evolved[26] (3 h). Then, the crude reaction mixture was poured into water, dried over magnesium sulphate and concentrated under vacuum. The residue was purified by flash chromatography (93:7 hexane:ether) to give 7 as a colorless oil (2.72 g, 80%). IR: ν = 1720 cm^{-1}. ^{1}H NMR: δ = 5.12(br t,1H,J=6Hz); 2.6-2.25(complex, 6H); 2.14(br,5H); 1.6-1.55(complex,9H). ^{19}F NMR: δ = -35.8(t,J=21Hz). MS: m/e= 212(M$^+$); 192(M$^+$-HF).
Calculated for $C_{13}H_{21}FO$: C=73.53;H=9.97. Found: C=73.60;H=9.83.

Methyl 10-fluorofarnesoate (8).
A solution of dimethyl methoxycarbonylmethylphosphonate (5.15 g, 28 mmol) in benzene (30 ml) was added to a suspension of sodium hydride (0.67 g, 28 mmol) in the same solvent (50 ml) and the

mixture was stirred for 1 h at 25°C. Then a solution of ketone 7 (1.50 g, 7.1 mmol) in benzene (10 ml) was added dropwise. The crude reaction mixture was stirred for 12 h at 60°C, cooled and poured into a 0.1 N hydrochloric acid solution (100 ml), and extracted with pentane (3x50 ml). The organic extracts were washed with water and dried over magnesium sulphate. The residue obtained after solvent elimination (1.90 g, of a 76:24 2E,2Z isomeric mixture of 8, GLC) was purified by preparative thin layer chromatography on silicagel (three elutions with 100:3 hexane:ether solution), to afford the 2E,6E isomer (705 mg, 74%) and the 2Z,6E isomer (224 mg, 23%) as pure compounds.

8 (2E,6E) IR: ν= 1725; 1645; 1225; 1150 cm^{-1}. ^1H NMR: δ = 5.72(q,1H,J=1.5Hz); 5.12(br t,1H, J=7Hz); 3.72(s,3H); 2.7-2.3(complex,2H); 2.2(br,9H); 1.65-1.55(complex,9H). ^{19}F NMR: δ= -36.4 (t,J=22Hz). ^{13}C NMR: δ= 167; 159.6; 154(d,J=242Hz); 135; 124; 115; 107(d,J=18Hz); 50.5; 40.7; 36.5; 27.6(d,J=29Hz); 25.9; 18.6; 17.3(d,J=6Hz); 15.7; 15.3(d,J=9Hz). MS: m/e= 268(M^+); 248(M^+ -HF); 237(M^+-OCH_3).

Calculated for $C_{16}H_{25}FO_2$: C=71.64;H=9.40. Found: C=71.72;H=9.36.

8 (2Z,6E) IR: ν= 1720; 1650; 1225; 1150 cm^{-1}. ^1H NMR: δ = 5.68(br,1H); 5.12(br t,1H,J=6Hz); 3.72(s,3H); 2.8-2.0(complex,8H); 1.92(d,3H,J=1Hz); 1.65-1.55(complex,9H).

Epoxidation assays on fluorofarnesoate 8.

A solution of ester 8 (2E,6E isomer, 0.027 g, 0.1 mmol) in dichloromethane (20 ml), maintained at the given temperature (see Table 1) was treated with a solution of an equimolecular amount of m-chloroperoxybenzoic acid (0.022 g) in the same solvent (10 ml). The mixture was stirred until TLC or GC analysis showed no more conversion of starting compound. Then, activated potassium fluoride (0.024 g, 0.4 mmol) was added and the crude reaction mixture was stirred for 15 min at 25°C and filtered. The process was repeated to ensure the complete elimination[27] of aromatic acids. Finally, evaporation of solvent afforded a residue containing the corresponding mixture of unreacted ester 8 and of epoxides at C10-C11 (9) and at C6-C7, which was quantified by ^{19}F NMR (see Table 1).

Likewise, an epoxidation carried out with 0.54 g (2 mmol) of 8 and working at 45°C, led to a residue (0.55 g), which was purified by flash chromatography on 400 mesh silicagel (9:1 hexane:ether) to give the 10,11-epoxiderivative 9 (0.17 g, 30%).

10,11-epoxiderivative ^1H NMR: δ= 5.82(q,1H,J=1.5Hz); 5.05(complex,1H); 3.78(s,3H); 2.9-2.0 (complex,4H); 2.15(d,3H,J=1.5Hz); 1.9-1.6(complex,2H); 1.63(br,3H); 1.5-1.1(complex,2H); 1.23(br, 6H). ^{19}F NMR: δ= -60.9(t,J=14Hz). MS: m/e= 284(M^+); 266(M^+-H_2O); 264(M^+-HF).

6,7-epoxiderivative ^1H NMR: δ= 5.72(q,1H,J=1Hz); 3.68(s,3H); 2.73(t,1H,J=6Hz); 2.6-2.0(complex, 4H); 2.19(d,3H,J=1Hz); 1.9-1.5(complex,4H); 1.65-1.55(complex,6H); 1.25(s,3H). ^{19}F NMR: δ = -36.8(t,J=5Hz). MS: m/e =284(M^+); 266(M^+-H_2O); 264(M^+-HF).

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ACKNOWLEDGEMENTS.- Financial support from CAICYT (Grant 84/0087) and CSIC (Grant 85/263) is gratefully acknowledged.