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SYNTHESIS OF DIENIC FLUORINATED ANALOGS OF INSECT SEX PHEROMONES

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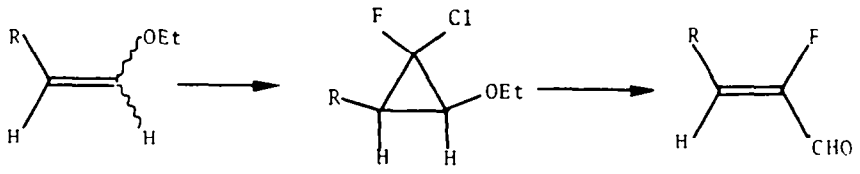
Abstract.- Synthesis of fluorinated analogs of some dienic insect sex pheromones through a stereocontrolled Wittig reaction of β-fluorinated aldehydes with the appropriate ω-functionalized ylides is reported. Some features of the ^{1}H and ^{19}F NMR spectra of these analogs are also discussed.

Incorporation of fluorine into bioactive organic molecules has been shown to mimic or inhibit the action or their non-fluorinated analogs.[1,2] In this context, substitution of a fluorine atom for hydrogen in insect sex pheromones could be expected to interfere the perception of the natural pheromone by competitive binding of the fluorinated analogs with specific pheromone receptors, eventually leading to the disruption of the mating communication system.[3] Furthermore, the above substitution could increase the thermal and oxidative stability of the parent compounds, which might be of potential interest in field trials.

In this paper, we describe the synthesis of fluorinated analogs of some dienic insect sex pheromones, in which a vinyl hydrogen has been replaced by fluorine. The preparation of these fluorinated compounds, so far unreported in the literature, is based on the stereocontrolled Wittig reaction of an α,β-unsaturated α-fluoroaldehyde, of defined stereochemistry, with the required ylide.

As an appropriate representative of a Z,Z fluorinated dienic system, we selected (9Z,11Z)-11-fluorotetradecadien-1-yl acetate 1, a fluorinated mimic of the sex pheromone of the Egyptian cotton leafworm *Spodoptera littoralis* Boisd[4] and (3Z,5Z)-5--fluorotetradecadien-1-yl acetate 2, fluorinated analog of the sex pheromone of the carpenterworm *Prionoxystus robiniae*.[5] For preparation of these compounds, we used as fluorinated synthons the unsaturated fluoroaldehydes 8a[6] and 8b, easily available by cyclopropanation of the corresponding enol ethers 6a and 6b, under PTC conditions,[7] or in the presence of potassium t-butoxide,[8] followed by stereoselective ring opening reaction of the resulting cyclopropanes 7a and 7b, in 45-50% overall yields[9] (Scheme 1).

When compound 8a was subjected to Wittig reaction under "salt-free" conditions with the tetrahydropyranyl derivative of 9-hydroxynonyltriphenylphosphonium bromide 9a, the expected compound 10a was obtained in 64% yield in a 92/8 Z,Z/E,Z isomer ratio.[10] On the other hand, the use of the corresponding free alcohol 9b afforded only 48% of compound 10b in a slightly lower isomer ratio (Z,Z/E,Z 88/12)(Scheme 2).



6a: R=C_2H_5 7a: R=C_2H_5 8a: R=C_2H_5

6b: R=C_8H_{17} 7b: R=C_8H_{17} 8b: R=C_8H_{17}

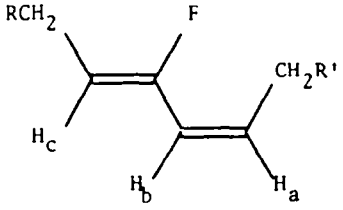
6c: R=H 7c: R=H 8c: R=H

6d: R=CH_3 7d: R=CH_3 8d: R=CH_3

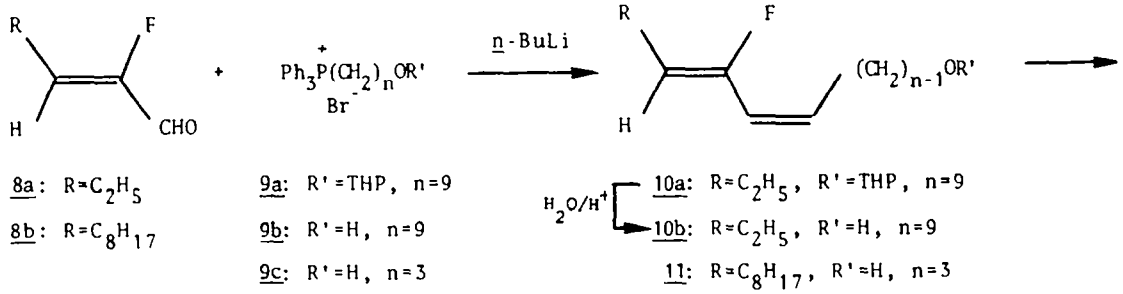
Scheme 1

Likewise, reaction of aldehyde 8b with the ylide derived from alcohol 9c yielded only 20% of the expected compound 11 (Z,Z/E,Z 34/66). The alternative use of the THP derivative of alcohol 9c in the Wittig reaction has so far not been possible since trials to protect the free alcohol as its tetrahydropyranyl, acetyl, trimethylsilyl or t-butildimethylsilyl derivatives proved to be unsuccessful. Acetylation under standard conditions of the corresponding alcohols 10b and 11 furnished the expected acetates 1 and 2 in good yields (Scheme 2).

The ^1H NMR spectra of 1 and 2 showed the expected characteristic pattern of a Z,Z dienic conjugated fluorinated system



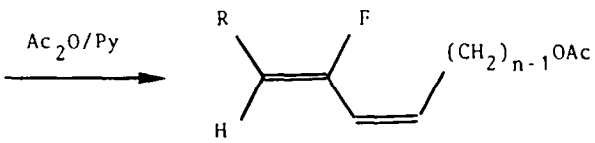
Thus, for compound 1, H_c was assigned to a doublet of triplets centered at δ 4.73 with coupling constants J=35.50 Hz (J_{Hc-F} trans) and 7.69 Hz (J_{Hc-CH_2R}), H_a, similarly, to a doublet of triplets at δ 5.39 with J=11.81 Hz (J_{Ha-Hb} cis) and 7.37 Hz ($J_{Ha-CH_2R'}$) and, finally, H_b to a doublet of doublets[11] at δ 5.62 with J=28.38 Hz (J_{Hb-F}).



8a: R=C_2H_5 9a: R'=THP, n=9 10a: R=C_2H_5, R'=THP, n=9

8b: R=C_8H_{17} 9b: R'=H, n=9 10b: R=C_2H_5, R'=H, n=9

9c: R'=H, n=3 11: R=C_8H_{17}, R'=H, n=3

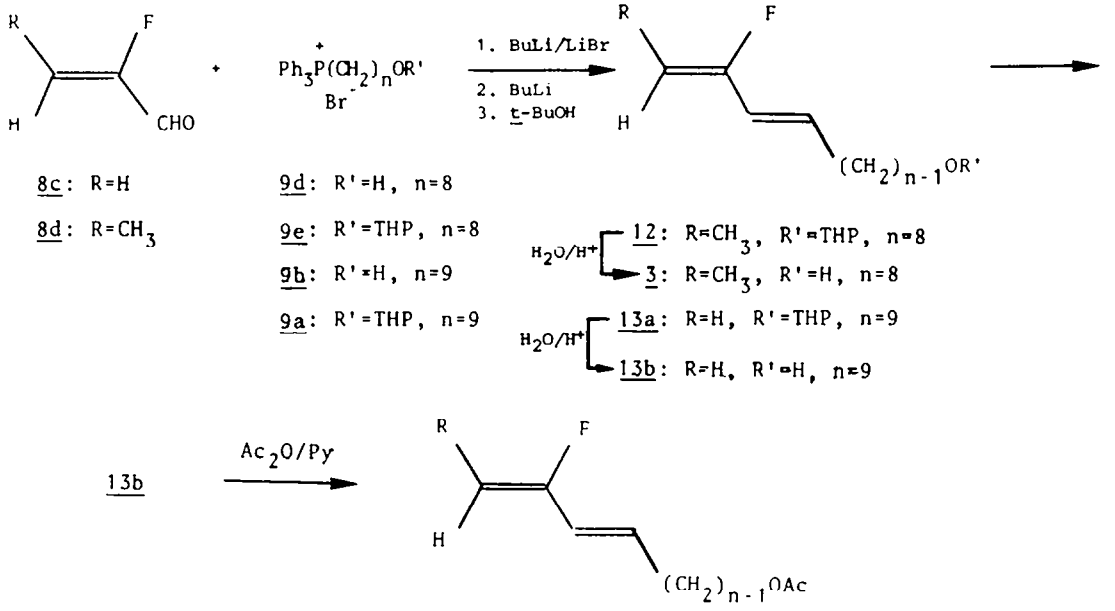


1: R=C_2H_5, n=9

2: R=C_8H_{17}, n=3

Scheme 2

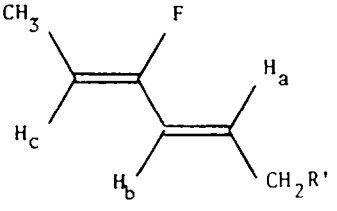
Likewise, as a representative example of a fluorinated dienic E,Z system, we chose the fluorinated analog of the sex pheromone of the codling moth *Laspeyresia pomonella* L. 3. In this case, fluoroaldehyde 8d[7] was allowed to react with the required ylide under the Schlosser modification,[12] which implies addition of one equivalent of n-BuLi to the previously formed betaine in the presence of a lithium salt (Scheme 3).



Scheme 3

When the reaction was carried out with the ylide of the free alcohol 9d, only 37% yield of the expected compound 3 was obtained, being the Z,Z/E,Z isomer ratio 15/85 by GC analysis. It is noteworthy that protection of the alcohol as its THP ether increased the yield of 3 to 58% and notably improved the stereochemical course of the reaction (Z,Z/E,Z 4/96). Stereochemically pure E,Z-3 was accomplished by crystallisation of the isomeric mixture at -30°C in pentane.

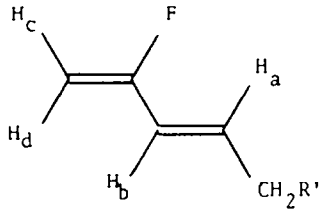
Again, the ^{1}H NMR spectrum of 3 exhibited the expected features of the E,Z dienic conjugated system



Thus, the H_c signal appeared as a doublet of quadruplets centered at δ 4.67 with coupling constants J_{Hc-F}=36.85 Hz, indicating a trans configuration, and J_{Hc-CH_3}=7.23 Hz. The doublet of doublets signal of H_b appeared at δ 5.75 with coupling constants J_{Hb-F}=24.05 Hz and J_{Hb-Ha}=15.59 Hz (trans configuration). Finally, the multiple absorption centered at δ 5.89 was assigned to proton H_a and interpreted as a partially overlapping doublet of triplets (J_{Ha-Hb}=15.59 Hz, J_{Hz-CH_2}=7.0 Hz).

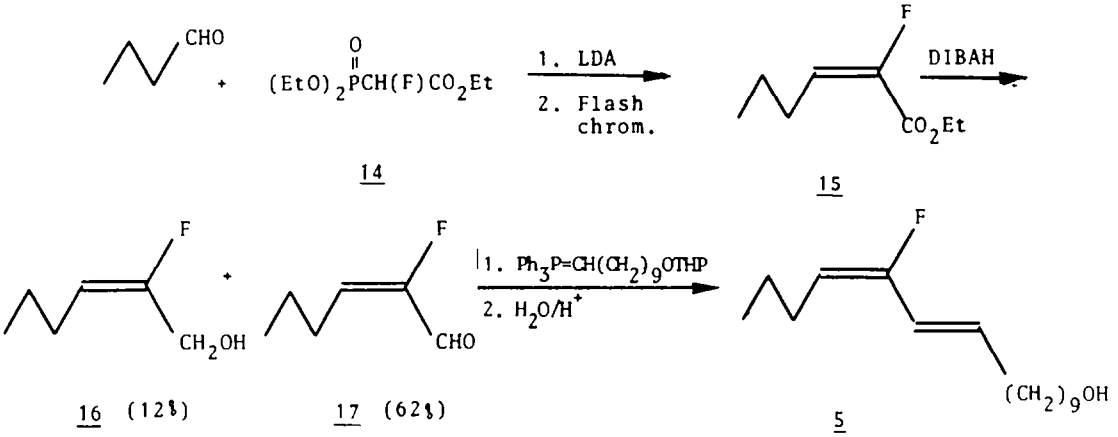
Similarly, preparation of the fluorinated analog of the sex pheromone of the red bollworm moth *Diparopsis castanea* Hampson[4] 4, was accomplished by the same sequence depicted above (Scheme 3), starting from the rather unstable fluoroacrolein 8c.

The ^1H NMR spectrum of 4 was in agreement with the expected pattern of a E fluorinated conjugated dienic system of the type



The two terminal vinyl protons H_c and H_d appeared as a doublet of doublets at δ 4.56 and 4.32 ppm, with coupling constants J_{Hd-F}=49.3 Hz, J_{Hc-F}=16.65 Hz and J_{Hc-Hd}=2.54 Hz. On the other hand, H_b absorption displayed a doublet of doublets[11] centered at δ 5.83 with coupling constants J_{Hb-F}=24.76 Hz and J_{Hb-Ha}=15.66 Hz, whereas H_a showed a doublet of triplets at δ 6.07 with J_{Ha-Hb}=15.66 and J_{Ha-CH_2}= =6.74 Hz.

Finally, we undertook the synthesis of a fluorinated mimic of the sex pheromone of the silkworm moth *Bombyx mori*[13] 5, as an appropriate model of a E,E dienic system. Wittig-Horner reaction of lithium triethylphosphonofluoroacetate,[14] 14, with butyraldehyde afforded ester 15 (85%) in a Z/E 9/91 isomer ratio on GLC analysis (OV-101, 3% on Chr. W, 80°C).[15] Purification of the E isomer by flash chromatography,[16] eluting with hexane-ethyl acetate mixtures, yielded isomerically pure ester E-15. Reduction of 15 with DIBAH at low temperature[17] afforded stereospecifically fluoroaldehyde 17 in 62% yield along with 12% of the corresponding alcohol 16, as determined by GLC analysis. Aldehyde 17, being highly prone to isomerization into the thermodinamically more stable trans isomer, was immediately subjected to the Schlosser modification of the Wittig reaction with the THP derivative of 10-hydroxydecyltriphenylphosphonium bromide, to achieve, after acid hydrolysis, compound 5 in 62% yield, as a mixture of isomers (E,Z/E,E/Z,Z/Z,E 63/23/14/<1) according to GLC analysis[10] and the ^{19}F NMR spectrum. Thus, the four clusters of signals at δ -30.58, -37.11, -39.69 and -45.64 ppm, upfield relative to TFA, were assigned unequivocally to the Z,E, Z,Z, E,E, and E,Z isomers, respectively, by comparison with those of isomerically pure analogs as well as by the magnitude of the corresponding coupling constants. In this context, the doublets of doublets at δ -30.58



Scheme 4

(J=29.40 and 22.61 Hz) and δ -37.11 (J=36.18 and 27.14 Hz) were attributed to dienic systems where the C-10 double bonds are in cis position, since no J_{F-CH_2} was observed in these absorptions. The coupling constants J=22.61 and 36.18 Hz point out, respectively, to cis and trans H-C=C-F arrangements, leading finally to the Z,E and Z,Z assignments of the above absorptions. Similarly, the high field pair of complex absorptions at δ -39.69 and -45.64 could be assigned to the E,E and E,Z isomers respectively. These absorptions, which displayed basically a doublet of doublets pattern, showed further coupling with a methylene group, apparently the CH_2 at C-9, as observed for other products mentioned previously.

The ^{19}F NMR spectra of the fluorinated mimics 1-5 exhibited different features whether the non-fluorinated double bond is Z or E. Thus, spectra of compounds 1 and 2, which belong to the former type, simply showed the expected doublet of doublets by coupling of fluorine with the corresponding vicinal hydrogens (J=35.5 and 28.38 Hz for compound 1 and J=36.2 and 29.5 Hz for 2), whereas spectra of compounds 3, 4 and 5, with E configuration on the non-fluorinated double bond, displayed further coupling with allylic protons through a sp^2-extended zig-zag long range interaction.[18]

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin Elmer 257 spectrometer. ^1H NMR spectra were determined in $CDCl_3$ on a Bruker WP80SY operating at 80 MHz or on a Varian XL200 spectrometer operating at 200 MHz. ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker WP80SY working at 20.15 MHz 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 (TFA) was used as external standard in the ^{19}F NMR spectra. High resolution mass spectra by direct inlet injection mode were taken on a AEI MS-9 spectrometer and low resolution mass spectra on a Hewlett Packard 5993 coupled with a gas chromatograph. Elemental analyses were determined on a Carlo Erba 1106. Gas chromatographic (GLC) analyses were performed on Carlo Erba models 2350 and 4130, equipped with a FID detector, using 3% OV-101 glass column 2m x 1/8" i.d. on Chromosorb W (N_2 as carrier gas), or a fused silica capillary column SE-54 50m x 0.32mm i.d. (H_2 as carrier gas). UV spectra were run on a Uvikon 820 spectrometer.

Reaction requiring anhydrous conditions were performed under inert (N_2 or Ar) atmosphere. THF and ether were distilled from Na/benzophenone under N_2. Anhydrous CCl_4 was prepared by distillation over P_2O_5 and anhydrous pyridine by distillation over KOH. Anhydrous HMPT was prepared by distillation from CaH_2.

Preparation of cyclopropanes 7a-c

Following the same cyclopropanation procedure described by Y. Bessière et al.[7], but with longer reaction times, were prepared:

1-Chloro-2-ethoxy-3-ethyl-1-fluorocyclopropane 7a. - Starting from the required (Z/E)-1-ethoxy-1-butene, compound 7a was obtained in 80% yield as a mixture of diastereoisomers, b.p. 43-45°/65 Torr. IR (CCl_4) ν 2960, 2930, 1290, 1130 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 3.25-3.9 (c, 3H, $CHOCH_2CH_3$), 1.5 (c, 3H, $CH-CH_2CH_3$), 1.23 (t J=7.2 Hz, 3H, OCH_2CH_3), 1.05 (t J=7.2 Hz, 3H, $C-CH_2CH_3$). ^{19}F NMR ($CDCl_3$) -56.25 (ddt, J=26.79, 12.75 and 2.39 Hz), -57.61 (ddt, J=32.08, 17.58 and 2.05 Hz), -75.16 (bd, J=24.35), -75.53 (bd, J=13.69 Hz). Anal. Calcd. for $C_7H_{12}ClFO$: C, 50.45; H, 7.20. Found: C, 50.19; H, 7.12.

1-Chloro-2-ethoxy-1-fluoro-3-octylcyclopropane 7b.- Following the same procedure[7], starting from (Z/E)-1-ethoxy-1-decene, compound 7b was prepared (61%) as a mixture of diastereoisomers, b.p. 90-95°/0.55 Torr. IR (CCl_4) ν 2960, 2930, 2860, 1290 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 3.3-3.9 (c, 3H, $CHOCH_2CH_3$), 1.02-1.7 (b, 21H, $C-CH_2-C$, OCH_2CH_3 and $CHCH_2$), 0.89 (t, 3H, CH_2CH_3). ^{19}F NMR ($CDCl_3$) -56.18 (dd, J=23.00 and 12.77 Hz), -58.14 (dd, J=32.36 and 18.01 Hz), -74.77 (bd, J=14.64 Hz), -75.03 (bd, J=24.75 Hz). Anal. Calcd. for $C_{13}H_{24}ClFO$: C, 62.40; H, 9.60. Found: C, 62.72; H, 9.91.

1-Chloro-2-ethoxy-1-fluorocyclopropane 7c.- Starting from ethyl vinyl ether, cyclopropane 7c was prepared in 76% yield as a mixture of diastereoisomers, b.p.53-55°C/120 Torr. IR (CCl_4) ν 1210 (C-O), 1385 (C-F) cm^{-1}. ^1H NMR 80 MHz ($CDCl_3$) δ 1.24 (t J=7.02 Hz, 3H, $O-CH_2-CH_3$), 1.1-1.9 (c, 2H, $CH-CH_2-C$), 2.3-2.9 (c, 3H, $CHOCH_2CH_3$). ^{19}F NMR ($CDCl_3$) -61.94 (ddd, J=20.36, 12.77 and 7.67 Hz) -83.07 (dd, J=18.0 and 10.0 Hz). Anal. Calcd. for C_5H_8ClFO: C, 43.47; H, 5.79. Found: C, 43.88; H, 5.99.

1-Chloro-2-ethoxy-1-fluoro-3-methylcyclopropane 7d. - This compound has been already described[7] ^{19}F NMR ($CDCl_3$) -57.34 (ddq, J=22.33, 13.37 and 2.66 Hz), -58.66 (ddq, J=31.79, 18.11 and 2.63 Hz), -75.95 (bd, J=13.31 Hz), -76.40 (bd, J=22.97). These values differ notably from those reported[7]

Preparation of fluoroaldehydes 8a-d

Ring opening reaction of the corresponding cyclopropanes 7a-d has been applied to obtain fluoroaldehydes 8a-d according to the literature[7]

(Z)-2-fluoro-2-pentenal 8a.- Yield 61%, b.p. 54-56°C/20 Torr. IR (CCl_4) ν 1700, 1655, 1350, 860 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 1.15 (t J=7.3 Hz, 3H, CH_3), 2.30 (dqi, 2H, $CH_2C=C$), 5.98 (dt J=32.6 and 8.0 Hz, 1H, $HC=C$), 9.21 (d J=18.0 Hz, 1H, CHO). ^{13}C NMR 183.39 (C-1), 155.84 (C-2), 132.38 (C-3), 17.83 (C-4), 12.17 (C-5). ^{19}F NMR ($CDCl_3$) -55.60 (dd, J=32.7 and 18.1 Hz) (further coupling with the allylic methylene group can also be observed). MS m/z (relative intensity) 102 (9.4), 73 (11.8), 58 (46.4), 53 (23.9), 44 (11.9), 43 (100). Exact mass calcd. for C_5H_7FO 102.048095; Found 102.047989.

(Z)-2-Fluoro-2-undecenal 8b.- Yield 79%, b.p.100-105°/0.3 Torr. IR (CCl_4) ν 1710, 1660, 1465 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 0.90 (t, 3H CH_3), 1.31 (b, 12H, $C-CH_2-C$), 2.10-2.60 (c, 2H, $CH_2-C=C$), 5.94 (dt J=32 and 7.3 Hz, HC=C), 9.20 (d J=17.5 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$) 183.27 (C-1), 156.44 (C-2), 130.90 (C-3), 21.90 (C-4), 24.41 (C-5), 24.52 (C-6), 28.01 (C-7), 28.99 (C-8), 31.62 (C-9), 22.39 (C-10), 13.72 (C-11). Assignments corresponding to carbons with close chemical shift may be interchanged. ^{19}F NMR ($CDCl_3$) -55.35 (dd, J=32.2 and 18.0 Hz) (an apparent triplet of very small coupling constant was also observed). MS m/z (relative intensity) 100 (10.7), 94 (16.8), 87 (66.0), 81 (13.2), 80 (21.6), 69 (15.1), 68 (55.7), 66 (13.7), 58 (14.7), 57 (21.6), 56 (66.1), 55 (16.6), 54 (46.5), 42 (100), 41 (14.2). Elemental analysis was determined as its 2,4-dinitrophenylhydrazone. Calcd. for $C_{17}H_{23}FN_5O_6$: C, 49.51; H, 5.58; N, 16.99. Found: C, 49.93; H, 5.80; N, 17.03.

2-Fluoro-2-propenal 8c .- For preparation of this compound a slight modification of the reported procedure has been applied, as follows. A mixture of 1-chloro-2-ethoxy-1-fluorocyclopropane 7c (17 gr, 0.123 mole) and hydroquinone (ca. 50 mg) was added to 30 ml of a 0.015M solution of sodium dodecylsulfate in water. The mixture was heated to reflux for 14 hrs and fractionally distilled over a period of 6 hrs, to afford a mixture of the expected aldehyde and unreacted cyclopropane 7c. Careful redistillation of this mixture over a small amount of hydroquinone yielded 3.45 gr (38%) of the rather unstable 2-fluoro-2-propenal, b.p. 80-85°C. IR (CCl_4) ν 1715, 1680, 1640, 1170 cm^{-1}. ^1H NMR 80 MHz (CCl_4) 5.36 (dd H=29.7 and 3.0 Hz, 1H, HC=CF trans), 5.84 (dd J=4.75) and 3.0 Hz, 1H, HC=CF cis), 9.4 (d J=14.6 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$) 188.64 (C-1), 130.73 (C-2), 107.44 (C-3). ^{19}F NMR ($CDCl_3$) -44.1 (ddd, J=30.0, 14.3 and 5.2). Elemental analysis was determined as its 2,4-dinitrophenylhydrazone. Calcd. for $C_9H_7FN_4O_4$: C, 42.51; H, 2.75; N, 22.04. Found: C, 42.34; H, 2.88; N, 21.54.

(Z)-2-Fluoro-2-butenal 8d.- This compound has already been reported[7] ^{13}C NMR ($CDCl_3$) 183.58 (C-1), 157.20 (C-2), 126.66 (C-3), 9.87 (C-4). ^{19}F NMR ($CDCl_3$) -58.91 (ddq, J=32.06, 18.41 and 2.56 Hz).

(9Z,11Z)-11-fluorotetradecadien-1-ol 10b. In a 3-neck round-bottomed flask were placed 1.6 gr (2.77 mmole) of 9-tetrahydropyranyloxynonyl triphenylphosphonium bromide 9a, previously dried at 100°C/0.1 Torr, dissolved in a mixture of 25 ml of anhydrous THF and 5 ml of anhydrous HMPT. To this solution, previously cooled to -40°C, was added, under N_2, 2.34 ml of a 1.18M soln. of n-BuLi in hexane (2.77 mmole). Stirring was continued for 30 min and the solution further cooled to -76°C. (Z)-2-Fluoro-2-pentenal, 8a, (0.16 gr, 1.6 mmole) in 2 ml of anhydrous THF was added and the mixture stirred 1 hr at -76°C and 3 hrs at room temperature. The reaction mixture was, then, poured into ice-water and extracted with hexane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum to yield 1.02 gr of an oil, characterized as 10a by its spectroscopic properties. Compound 10a was diluted with methanol and refluxed for 17 hrs in the presence of a catalytic amount of p-toluensulfonic acid. After this period of time, powder Na_2CO_3 was added and the mixture stirred for 15 min. The solvent was evaporated ant the residue extracted with ether, washed with brine and dried ($MgSO_4$). Removal of the solvent and purification on column chromatography (florisil), eluting with hexane/ether 95/5 afforded 241 mg (64%) of alcohol 10b of 95/5 Z,Z/E,Z isomeric purity by GLC analysis[10] IR (CCl_4) ν 3640, 3350, 2930, 2860, 1455, 1215, 910 cm^{-1} ^1H NMR 200 MHz ($CDCl_3$) δ 0.99 (t J=8.0 Hz, 3H, CH_3), 1.30-1.60 (b, 12H, $C-CH_2-C$), 1.97 (b, 1H, OH), 2.18 (c, 2H, CH_2CH_2C), 2.42 (q J=6.3 Hz, 2H, $CH_2CH_2C=C$), 3.64 (t J=8.0 Hz, 2H, CH_2OH), 4.73 (dt J=36.11 and 7.69 Hz, 1H, CH=CF), 5.39 (dt J=11.81 and 7.37 Hz, 1H, CH=CH-CF), 5.62 (dd J=29.60 and 11.81 Hz, 1H, CH=CH-CF). MS m/z (relative intensity) 228 (M^+, 9.8), 114 (30.4), 100 (45.7), 99 (35.7), 98 (20.5), 97 (73.1), 96 (20.1), 93 (28.3), 91 (26.5), 85 (100), 82 (21.5), 81 (21.7), 79 (29.4), 77 (23.9), 67 (32.2). Anal. Calcd. for $C_{14}H_{25}FO$: C, 73.68; H, 10.96. Found: C. 74.08; H, 10.83.

(9Z,11Z)-11-Fluorotetradecadien-1-yl acetate 1.- To a solution of alcohol 10b in 3 ml of anhydrous CCl_4 were added acetic anhydride (1 ml) and anhydrous pyridine (1 ml). The mixture was stirred at room temperature until no starting material remained by GLC analysis (4 hrs). Methanol (3 ml) was added and the solution further stirred for 20 min. Evaporation of the solvent left a residue which was taken up in CH_2Cl_2, washed sequentially with 2N HCl, $NaHCO_3$ sat. soln. and brine and dried. Removal of the solvent yielded 0.1 gr (80%) of acetate 1, which was purified by bulb-to-bulb distillation, b.p. 100-105°C/0.1 Torr. (95/5 Z,Z/E,Z isomer ratio). IR (CCl_4) ν 2930, 2860, 1735, 1665, 1235 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 1.01 (t J=7.3 Hz, 3H, CH_2CH_3), 1.20-1.80 (b, 12H, $C-CH_2-C$), 2.02 (s, 3H, $COCH_3$), 2.19 (c, 4H, $CH_2C=C$), 4.02 (t J=6.0 Hz, 2H, CH_2OCO), 4.68 (dt J=35.5 and 7.3 Hz, 1H, CH=CF), 5.1-6.0 (c, 2H, CH=CH). ^{13}C NMR ($CDCl_3$) 64.51 (C-1), 28.56 (C-2), 24.86 (C-3), 29.06 (C-4), 29.22 (C-5), 29.06 (C-6), 29,77 (C-7), 28.56 (C-8), 132.75 (C-9), 120.38 (C-10), 157.08 (C-11), 112.72 (C-12), 17.33 (C-13),13.88 (C-14), 170.96 (C-1'), 20.81 (C-2'). ^{19}F NMR ($CDCl_3$) -40.71 (dd, J=35.5 and 28.38 Hz). UV (pentane) λ 233 nm. Anal. Calcd. for $C_{16}H_{27}FO_2$: C, 71.11; H, 10.0. Found: C, 70.99; H, 9.97.

(3Z,5Z)-5-Fluorotetradecadien-1-ol 11.- To a suspension of 897 mg (2.44 mmole) of 3-hydroxypropyltriphenylphosphonium chloride in 25 ml of anh. THF and 5 ml of anh. HMPT were added at -76°C, under Ar, 4 ml of a 1.18M soln. of n-BuLi in hexane (4.88 mmole). The mixture was stirred for 30 min at this temperature and a solution of (Z)-2-fluoro-2-undecenal 8b (365 mg, 1.9 mmole) was added. Stirring was kept for 1 hr at -76°C and 3 hrs more at room temperature. Work-up as for compound 10b yielded alcohol 11 as an oil, which was purified by column chromatography on silica gel to afford pure 11 in 20% yield (Z,Z/E,Z 34/66 isomer ratio). IR (CCl_4) ν 3350, 2930, 2865, 1655, 1615, 1210, 905 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 0.88 (t J=7.2 Hz, 3H, CH_3), 1.22 (b, 12H, $C-CH_2-C$), 2.09 (c, 2H, $CH_2C=CF$), 2.38 (q J=6.4 Hz, 2H, $CH_2CH=CH$), 3.70 (t J=7.2 Hz, 2H, CH_2OH), 4.68 (dt J=37.0 and 6.9 Hz, 1H, CH=CF), 5.3-6.2 (c, 2H, CH=CH). ^{19}F NMR ($CDCl_3$) (Z,Z)-isomer: -38.32 (dd, J=36.2 and 29.5 Hz), (E,Z)-isomer: -46.36 (dd, J=38.27 and 10.0 Hz) (further splitting was also observed but no simple interpretation was possible). Anal. Calcd. for $C_{14}H_{25}FO$: C, 73.68; H, 9.96. Found: C, 73.43; H, 9.83.

(3Z,5Z)-5-Fluorotetradecadien-1-yl acetate 2.- Acetylation of alcohol 11 was performed under the same reaction conditions depicted above to yield the expected acetate 2 (86%), b.p. 95-100°C/0.05 Torr. IR (CCl_4) ν 2935, 2865, 1740, 1260, 1230 cm^{-1} ^1H NMR 200 MHz ($CDCl_3$) δ 0.81 (t J=6.3, 3H, CH_3CH_2), 1.19 (b, 12H, $C-CH_2-C$), 2.07 (c, 2H, $CH_2CH=CF$), 1.98 (s, 3H, $COCH_3$), 2.38 (q J=6.2 Hz, 2H, $CH_2CH=CH$), 4.05 (t J=6.8, 2H, CH_2O), 4.73 (dt J=36.20 and 8.2 Hz, 1H, CH=CF), 5.31 (dt J=11.88 and

7.30 Hz, 1H, CH=CHCF), 5.68 (dd J=30.01 and 11.88 Hz, 1H, CH=CHCF). ^{19}F NMR (Z,Z)-isomer: -41.82 (dd, J=36.01 and 27.96 Hz), (E,Z)-isomer: -49.18 (dd, J=36.5 and 25.57 Hz) (further splitting was also observed but no simple interpretation was possible). UV (pentane) λ 232 nm. Anal. Calcd. for $C_{16}H_{27}FO_2$: C, 71.18; H, 10.08. Found: C, 71.01; H, 9.89.

(8E,10Z)-10-Fluorododecadien-1-ol 3.- To a suspension of 3.15 gr (5.6 mmole) of phosphonium salt 9e (previously dried at 100°C/0.1 Torr) and 0.49 gr (5.6 mmole) of LiBr in 40 ml of anh. THF, cooled to -50°C, were added 4.86 ml of a 1.15M solution of n-BuLi in hexane (5.6 mmole). Stirring was maintained during 30 min and aldehyde 8d (0.3 gr, 3.4 mmole), dissolved in 2 ml of anh. THF, added to the reaction mixture. After stirring at -55°C for 5 hrs, the reaction flask was cooled to -76°C. Then, 3 ml of 1.15M BuLi (3.45 mmole) were added and stirred for 1 hr more. The reaction was quenched by adding 3 ml of t-butyl alcohol at 0°C, poured into ice-water and extracted with hexane. The organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent yielded 1.25 gr of an oil 12, which was hydrolyzed with camphosulfonic acid in methanol, in the usual way, to afford, after purification on column chromatography (SiO_2), 0.40 gr (58%) of alcohol 3 as a mixture of stereoisomers (Z,E/E,E 6/94 by GLC analysis[10]). Spectroscopically pure (E,E)-isomer 3 could be obtained by crystallisation in pentane at -30°C. IR (CCl_4) ν 3620, 2940, 2860, 1120, 960 cm^{-1} ^1H NMR 220 MHz ($CDCl_3$) δ 1.15-1.60 (c, 10H, C-CH_2-C), 1.67 (dd J=7.2 and 2.1 Hz, 3H, CH_3), 2.08 (q J=6.49 Hz, 2H, CH_2CH=CH), 3.63 (t, J=6.6 Hz, 2H, CH_2OH), 4.67 (dq J=36.85 and 7.32 Hz, 1H, CH=CF), 5.75 (dd J=24.05 and 15.59 Hz, 1H, CH=CH-CF), 5.89 (dt J=15.59 and 7.0 Hz, 1H, CH=CH-CF. ^{13}C NMR ($CDCl_3$) 62.36 (C-1), 32.48 (C-2), 25.50 (C-3), 28.51 (C-4), 28.85 (C-5), 29.05 (C-6), 31.99 (C-7), 129.85 (C-8), 121.89 (C-9), 156.90 (C-10), 182.18 (C-11), 8.82 (C-12). ^{19}F NMR ($CDCl_3$) -49.17 (ddq, J=36.61, 26.45 and 2.21 Hz). MS m/z (relative intensity) 200 (M^+, 25.9), 112 (33.2), 111 (47.0), 109 (22.7), 100 (46.3), 99 (36.1), 98 (39.3), 97 (100), 96 (28.8), 95 (21.4), 93 (26.8), 86 (78.0), 85 (78.9), 81 (25.9), 79 (77.3), 77 (41.5), 67 (52.7). UV (pentane) λ 232 nm. Anal. Calcd. for $C_{12}H_{21}FO$: C, 72.07; H, 10.58. Found: C, 71.65, H, 10.35.

When the reaction was carried out with the non-protected alcohol 9d, only 37% yield of 3 was obtained (Z,Z/E,Z 15/85 by GC analysis[10]).

(9E,11)-11-Fluorododecadien-1-ol 13b.- The same procedure as described above for compound 3 was applied. Thus, starting from 3 gr (5.26 mmole) of phosphonium salt 9a and 0.118 gr (1.6 mmole) of fluoroaldehyde 8c, was prepared the corresponding intermediate 13a, which was hydrolyzed as usual to yield, after purification on column chromatography (florisil), 0.12 gr (38%) of pure alcohol 13b, in a E/Z 90/10 isomer ratio, since no absorption due to the (Z)-11-isomer was detected in its ^{19}F NMR spectrum. IR (CCl_4) ν 3615, 3350, 2930, 2860, 1660, 1620, 1215, 910, 840 cm^{-1} ^1H NMR 200 MHz ($CDCl_3$) δ 1.10-1.75 (c, 12H, C-CH_2-C), 2.18 (c, 2H, CH_2C=C), 3.64 (t J=6.5 Hz, 2H, CH_2OH), 4.32 (dd J=49.3 and 2.54 Hz, 1H, HC=CF trans), 4.56 (dd J=16.65 and 2.54 Hz, 1H, HC=CF cis), 5.83 (dd J=24.76 and 15.66, 1H, CH=CH-CF), 6.07 (dt J=15.66 and 6.74, 1H, CH=CH-CF). ^{13}C NMR ($CDCl_3$) 62.94 (C-1), 28.77 (C-2), 25.67 (C-3), 29.01 (C-4), 29.29 (C-5), 32.16 (C-6), 32.61 (C-7), 32.75 (C-8), 133.73 (C-9), 121.53 (C-10), 162.61 (C-11), 90.87 (C-12). ^{19}F NMR ($CDCl_3$) -32.54 (ddd, J=47.49, 24.76 and 16.58 Hz) (further splitting, probably with the allylic methylene group was displayed, but no simple first order interpretation was possible). MS m/z (relative intensity) 200 (M^+, 8.1), 99 (24.2), 98 (44.4), 97 (59.0), 96 (28.0), 95 (26.8), 93 (23.9), 86 (100), 85 (51.7), 82 (21.5), 81 (50.0), 79 (34.1), 72 (47.5), 69 (25.3), 68 (36.9), 67 (74.4), 65 (31.5). Anal. Calcd. for $C_{12}H_{21}FO$: C, 72.07; H, 10.58. Found: C, 71.86; H, 10.23.

(9E,11)-11-Fluorododecadien-1-yl acetate 4.- Acetylation of alcohol 13b was conducted under the same reaction conditions depicted above to yield the expected acetate 4 (83%), b.p. 75-80°C/0.08 Torr. IR (CCl_4) ν 2935, 2865, 1735, 1660, 1615, 1235, 910, 840 cm^{-1} ^1H NMR 80 MHz ($CDCl_3$) δ 1.15-1.80 (c, 12H, C-CH_2-C), 2.08 (c, 2H, CH_2C=C), 2.02 (s, 3H, $COCH_3$), 4.04 (t J=7.1 Hz, 2H, CH_2OCO), 4.30 (dd J=49.3 and 2.3 Hz, 1H, HC=CF trans), 4.61 (dd J=16.7 and 2.3 Hz, 1H, HC=CF cis), 5.5-6.3 (c, 2H, CH=CH). ^{13}C NMR ($CDCl_3$) 64.41 (C-1), 28,53 (C-2), 25.77 (C-3), 28.67 (C-4), 28.95 (C-5), 29.00 (C-6), 29.17 (C-7), 32.30 (C-8), 133.50 (C-9), 121.53 (C-10), 162.30 (C-11), 90.85 (C-12), 170.89 (C-1'), 20.75 (C-2'). ^{19}F NMR ($CDCl_3$) -35.6 (ddd, J=48.35, 25.64 and 16.94). UV (pentane) λ 234 nm.

Ethyl (E)-2-fluoro-2-hexenoate 15.- To a cooled solution of LDA (21.8 mmole) in 15 ml of anhydrous THF at -78°C, was added dropwise, under N_2, a solution of 5.3 gr (21.8 mmole) of triethylphosphonofluoroacetate 14[15] in 5 ml of anhydrous THF. Stirring was maintained at -78°C for 1 hr and after this time 1.5 gr (21 mmole) of butyraldehyde were added and further stirred for 1 hr more and 2 hrs at room temperature. The reaction mixture was quenched with water and extracted with hexane/ether 1/1. The organic extracts were washed with brine and dried to yield after evaporation of the solvent, 3.24 gr (90.5%) of crude ester 15 (E/Z 86/14 by GLC analysis on a OV-101 column). Separation of the isomers by flash chromatography[17] on silica gel eluting with hexane/ethyl acetate 96/4, afforded the following fractions: fractions 10-14 contained pure (E)-isomer (48%), fractions 15-18 gave a mixture of (E) and (Z)-15 (22%) and fractions 19-22 yielded pure (Z)-isomer (15%). An analytical sample of the isomeric mixture was purified by bulb to bulb distillation, b.p. 75-80°C/30 Torr. IR (CCl_4) ν 1730, 1220, 900 cm^{-1} Anal. Calcd. for $C_8H_{13}FO_2$: C, 60.08; H, 8.12. Found: C, 59.93; H, 8.48. (E)-15: ^1H NMR 80 MHz ($CDCl_3$) δ 0.96 (t J=6.72 Hz, 3H, CH_3CH_2), 1.32 (t J=6.83 Hz, 3H, CH_3CH_2O), 1,45 (c, 2H, $CH_2CH_2CH_3$), 2.47 (dq J=7.2 and 1.7 Hz, CH_2C=C), 4.27 (q J=6.72, 2H, CH_3CH_2O) 5.88 (dt J=21.72 and 7.28 Hz, 1H, CH=CF). ^{13}F NMR ($CDCl_3$) 160.99 (C-1), 147.21 (C-2), 123.25 (C-3), 27.38 (C-4), 22.49 (C-5), 14.06 (C-6), 61.15 (C-1'), 13.58 (C-2'). ^{19}F NMR ($CDCl_3$) -35.95 (d, J=21.49 Hz). MS m/z (relative intensity) 160 (M^+,23), 132 (75.3), 117 (43.7), 91 (100), 59 (35.5), 58 (21.3), 57 (32.0), 55 (24.3), 45 (26.1), 43 (34.7), 42 (90.5), 41 (54.1). (Z)-15: ^1H NMR 80 MHz ($CDCl_3$) δ 0.96 (t J=6.72 Hz, 3H, CH_3CH_2), 1.31 (t J=6.83 Hz, 3H, CH_3CH_2O), 1.45 (c, 2H, $CH_2CH_2CH_3$), 2.23 (dq J=7.3 and 1.68 Hz, CH_2C=C), 4.24 (q J=6.72 Hz, 2H, CH_3CH_2O), 6.11 (dt J=32.8 and 7.3 Hz, 1H, CH=CF). ^{13}C NMR ($CDCl_3$) 160.85 (C-1), 148.22 (C-2), 120.32 (C-3), 26.18 (C-4), 21.67 (C-5), 14.06 (C-6), 61.37 (C-1'), 13.58 (C-2'). ^{19}F NMR ($CDCl_3$) -27.53 (d, J=33.22).

(E)-2-Fluoro-2-hexenal 17.- To a solution of 0.446 gr (2.7 mmole) of ethyl (E)-2-fluoro-2-hexenoate 15 in 30 ml of anhydrous pentane, cooled to -76°C, was added, under Ar, 2.7 ml of a 1M solution of DIBAH in hexane (2.7 mmole). After disappearance of the ester (CGL), the reaction mixture was hydrolyzed with saturated NH_4Cl solution and extracted thoroughly with pentane. The joined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was partially removed at low

temperature to avoid isomerization of the double bond, to afford a concentrated solution of aldehyde 17, which was used directly in the next step. ^{1}H NMR 80 MHz ($CDCl_3$) δ 6.2 (dt J=18.66 and 8.3 Hz, 1H, H-C), 9.2 (d J=18.0 Hz, 1H, CHO). GLC analysis of an analytical sample of the crude indicated the presence of aldehyde 17 in 62% yield along with 12% of alcohol 16.

(10E,12E)-12-Fluorohexadecadien-1-ol 5.- Wittig reaction of (E)-2-fluoro-2-hexenal 17 (87 mg, 0.75 mmole) with the ylide derived from 10-tetrahydropyranyloxydecyltriphenylphosphonium bromide (0.58 gr, 1.0 mmol) was performed as described above for compound 3. Work-up as usual yielded an oil, which was subjected to acid hydrolysis (p-TsOH) to afford 128 mg (62%) of the title compound 5, after purification on column chromatography (florisil). GLC analysis on a SE-54 capillary column showed 5 as a mixture of stereoisomers (E,Z/E,E/Z,Z/Z,E 63/22/14/<1). IR (CCl_4) ν 3400, 2930, 2850, 1460, 1220, 860 cm^{-1} ^{1}H NMR 200 MHz ($CDCl_3$) δ 0.91 (t J=7.3 Hz, 3H, CH_3), 1.0-1.8 (c, 16H, C-CH_2-C), 1.8-2.4 (c, 4H, CH_2CH=CH and CH_2CH=CF), 3.64 (t J=6.7 Hz, 2H, CH_2OH), 4.64 (dt J=37.01 and 7.8 Hz, 1H, CH=CF of the (E,Z) isomer), 4.74 (dt J=36.89 and 7.6 Hz, 1H, CH-CF of the (Z,Z)-isomer), 5.03 (dt J=21.74 and 8.57 Hz, 1H, CH=CF of the (E,E)-isomer), 5.39 (dt J=13.56 and 7.34 Hz, 1H, CH=CH-CF of the (Z,Z)-isomer), 5,64 (ddt J=29.68, 12.31 and 0.81 Hz, 1H, CH=CH-CF of the (Z,Z)-isomer), 5.76 (dd J=24.12 and 15.62 Hz, 1H, CH=CH-CF of the (E,Z)-isomer), 5.78-6.19 (c, 3H, CH=CH-CF of the (E,E)-isomer amd CH=CH-CF of the (E,Z)-isomer). ^{19}F NMR ($CDCl_3$) (E,Z)-isomer: -45.64 (dd, J=36.18 and 26.38 Hz), (E,E)-isomer: -39.69 (dd, J=27.9 and 21.8 Hz), (Z,Z)-isomer: -37.10 (dd, J=36.19 and 27.14 Hz), (Z,E)-isomer: -30.60 (dd, J=36.19 and 22.62 Hz). The (E,E) and (E,Z)-isomers displayed further splitting, probably with CH_2 group(s), but no simple first order interpretation was possible. MS m/z (relative intensity) 256 (M^+, 17.6), 128 (20.6), 121 (21.3), 114 (25.6), 111 (21.7), 109 (28.5), 99 (42.2), 98 (30.6), 97 (77.5), 96 (35.9), 95 (30.0), 94 (43.7), 93 (30.5), 91 (28.3), 86 (24,8) 85 (100), 82 (24.2), 81 (38.1), 79 (44.8), 77 (22.9), 72 (40.1), 69 (20.9), 67 (41.5), 65 (21.0). Anal. Calcd. for $C_{16}H_{29}FO$: C, 75.07; H, 11.42. Found: C, 74.65; H, 10.98.

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References and Notes

1.- R. Filler; Chem. Tech., 4, 752 (1974).
2.- T.B. Patrick; J. Chem. Ed., 56, 228 (1979).
3.- Our preliminary biological studies with fluorinated analogs of insect sex pheromones have so far exhibited a possible synergistic effect enhancing the activity of the natural pheromones. (F. Camps, J. Coll, G. Fabriás, A. Guerrero and M. Riba; Experientia, in press.
4.- B.F. Nesbitt, P.S. Beevor, R.A. Cole, R. Lester and R.G. Poppi; Nature New Biology, 244, 208 (1973).
5.- J.D. Solomon, R.E. Doolittle and M. Beroza; Ann. Entomol. Soc. Am., 65, 1058 (1972).
6.- F. Camps, J. Coll, G. Fabriás, A. Guerrero and M. Riba; Tetrahedron Lett., 1983, 3387.
7.- Y. Bessière, D.N. Savary and M. Schlosser; Helv. Chim. Acta, 60, 1739 (1977).
8a- L.A. Last, E.R. Fretz and R.M. Coates; J. Org. Chem., 47, 3216 (1982).
8b- P. Amice, L. Blanco and J.M. Conia; Synthesis, 1976, 196.
9.- Assignment of Z configuration to the resulting aldehydes was based on a trans H-F coupling constant in the ^{19}F NMR spectra (J_{H-F}=32.6 and 32.4 Hz for 8a and 8b, respectively.
10.-By using a fused silica capillary column SE-54 50m, 0.32mm i.d.
11.-The H_b absorption system appeared further coupled to the allylic methylene group, with higher coupling constant for the outer bands (J=1.55 Hz for compound 1 and 1.35 Hz for compound 2; inner bands J=1.20 and 1.10 Hz for compounds 1 and 2, respectively).
12.-M. Schlosser and K. Christmann; Angew. Chem. Int. Ed., 5, 126 (1966).
13.-A. Butenandt, R. Bechmann and D. Stamm; Z. Physiol. Chem., 324, 71 (1961).
14.-R.S.H. Liu, H. Matsumoto, A.E. Asato, M. Denny, Y. Schichida, T. Yoshizawa and F.W. Dahlquist; J. Am. Chem. Soc., 103, 7195 (1981).
15.-Noticeably, the stereochemical course of this reaction is clearly reversed in comparison with the normal Wittig-Horner reaction, which gives, predominantly, the trans isomer (W.S. Wadsworth Jr; Org. React. 25, 73 (1977).
16.-W.C. Still, M. Kahn and A. Mitra; J. Org. Chem, 43, 2923 (1978).
17.-L.I. Iakhaskin and I.M. Khorlina; Tetrahedron Lett., 1962, 619.
18.-L.M. Jackman and S. Sternhell in "Application of NMR Spectroscopy in Organic Chemistry" 2nd. Ed. Pergamon Press, 1969.
19.-A. Barabas, A.A. Botar, A. Gocan, N. Popovici and F. Hodosan; Tetrahedron, 34, 2191 (1978).
20.-G.C. Levy in "Topics in C-13 NMR Spectroscopy" Vol. 2, John Wiley and Sons, 1976.