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A CONVENIENT AND STEREOSELECTIVE SYNTHESIS OF (3Z,5Z)-5-FLUOROTETRADECADIEN-1-YL ACETATE, A FLUORINATED ANALOG OF THE SEX PHEROMONE OF THE CARPENTERWORM *Prionoxistus robiniae* (PECK)

A. Alcazar, F. Camps*, J. Coll, G. Fabriàs and A. Guerrero.
Instituto de Química Bio-Orgánica (CSIC), Jorge Girona Salgado, 18
08034 Barcelona. SPAIN

Abstract: A convenient synthesis of (3Z,5Z)-5-fluorotetradecadien-1-yl acetate 1, a fluorinated analog of the sex pheromone of the carpenterworm *Prionoxistus robiniae* (Peck), through reaction of (Z)-2-fluoro-2-undecenal 4 with the previously unreported Wittig reagent 5,5-dimethyl-4,6-dioxaoctyltripenylphosphonium chloride 6, is presented.

The carpenterworm *Prionoxistus robiniae* (Peck) (Lepidoptera, Cossidae) is an important destructive pest of eastern hardwood forests. The sex pheromone produced by the female gland was identified by Doolitle et al.[1] as (3Z,5E)-tetradecadien-1-yl acetate 2 through laboratory bioassays (EAG) and field tests.

During our recent work on the synthesis of some dienic fluorinated analogs of insect sex pheromones,[2,3] we encountered serious difficulties in the preparation, in good yield and stereomeric purity, of the fluorinated mimic of the carpenterworm natural attractant (3Z,5Z)-5-fluorotetradecadien-1-yl acetate, 1.[2] In this

*To whom correspondence should be addressed.

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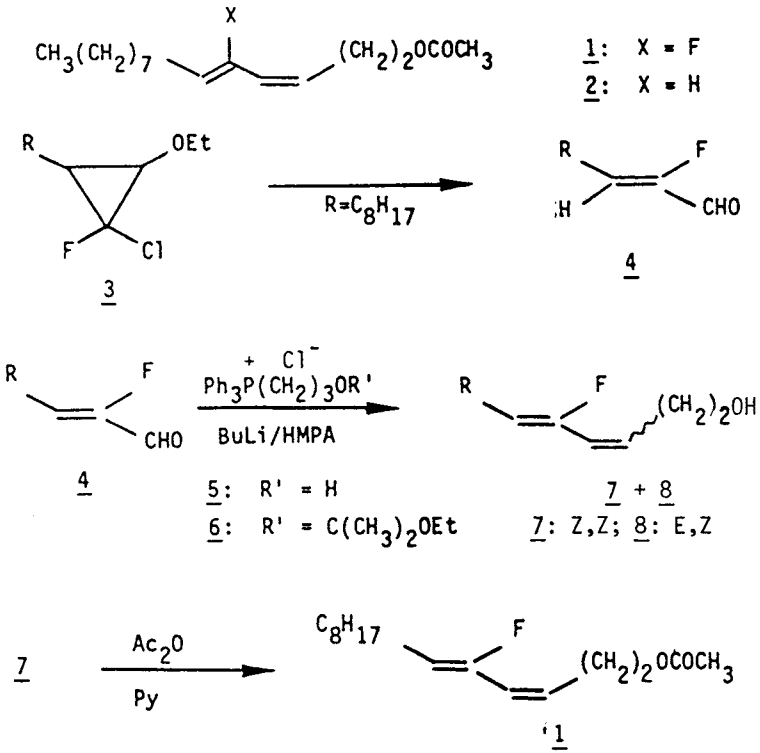
paper, we describe a convenient and stereoselective synthesis of this compound by reaction of the required α,β-unsaturated fluoroaldehyde 4[4] with the heretofore unreported Wittig reagent 5,5-dimethyl-4,6-dioxaoctyltriphenylphosphonium chloride 6 under "salt-free" conditions. Compound 6 was quantitatively prepared by reaction of the free alcohol 5 with 2-ethoxyprop-1-ene (Scheme 1).

Application of the Wittig reaction with the ylide derived from 3-hydroxypropyltriphenylphosphonium chloride 5 to the synthesis of insect sex pheromones has been reported.[1,5,6] However, this



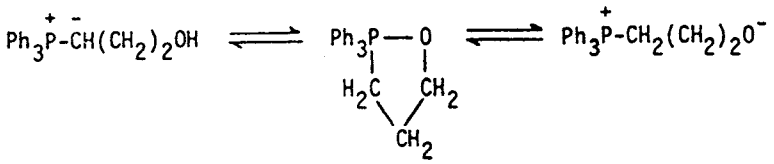
Scheme 1

reaction not only proceeds with poor stereoselectivity in the formation of the new double bond (Z:E 1:3 to 1:2) but with unsatisfactory yields as well (20-40%).[1,6] A presumable explanation for these drawbacks may arise from the partial oxaphospholan character of this ylide[7] (Scheme 2).

In order to obviate these difficulties, the protection of the free alcohol 5, previous to the generation of the ylide, was attempted (see Table).

As shown in the Table, reacion of 5 with dihydropyran (DHP) in the presence of p-toluenesulfonicacid (20ºC/16 hrs) (entry 1), with acetyl chloride (80ºC/3 hrs) (entry 2) or with t-butyldimethylsilyl chloride (20ºC/64 hrs) (entry 4) yielded only partial protection of the salt. On the other hand, treatment with trimethylsilyl chloride (80ºC/24 hrs) (entry 3) or with ethyl vinyl ether (EVE) in the presence of a trace of pyridinium p-toluenesulfonate (PPTS) (entry 5) led only to the recovery of unreacted starting material. Strikingly, in other cases when direct formation of the protected phosphonium salt was tried by reaction of triphenylphosphine with derivatized 3-halo-1-propanols, C-O and Si-O bonds cleavage was observed (entries 7, 8 and 9). Finally, successful protection of compound 5 was accomplished in excellent yield by treatment at -20ºC under argon with 2-ethoxyprop-1-ene[8], generated in situ by decarboxylation of 3-ethoxycrotonic acid[9] (entry 6).

The labile phosphonium salt 6 was subjected to a Wittig reaction with (Z)-2-fluoro-2-undecenal 4, obtained by ring opening reaction of the corresponding precursor cyclopropane 3,[4] under the best experimental conditions found for an optimum Z:E isomer ratio (butyllithium in THF:HMPT 5:1).[10] The intermediate protected adduct thus formed, was hydrolyzed in the working-up, avoiding an acid hidrolysis step and therefore conferring an additional advantage to 6 over other O-protected Wittig reagents. In this way, a 2:1 isomeric mixture of (3Z,5Z) and (3E,5Z)-5-fluorotetradecadien-1-ols (7 and 8) was obtained in 58% yield (GLC analysis on a SE-54 fused silica capillary column). On the other hand, as anticipated, when the reaction was carried out with the free alcohol 5, only a poor 22% yield of mixture of dienols 7 and 8 was obtained in 1:2 isomer ratio.[2]



Scheme 2

Table. Experiments conducted towards protection of phosphonium salt 5

Entry	Reagents	Reaction Product	Yield (%)
1	5 + DHP[1]	$Ph_3\overset{+}{P}(CH_2)_3OTHP\ Cl^-$	45
2	5 + AcCl	$Ph_3\overset{+}{P}(CH_2)_3OAc\ Cl^-$	40
3	5 + TMSCl	----	--
4	5 + t-BDMSCl	$Ph_3\overset{+}{P}(CH_2)_3Ot\text{-}BDMS\ Cl^-$	20
5	5 + EVE[2]	----	--
6	5 + $CH_3C(OEt)=CH_2$	6	100
7	Ph_3P + $Cl(CH_2)_3OTHP$[3,4]	5	40
8	Ph_3P + $Cl(CH_2)_3OTMS$[3,4]	5	95
9	Ph_3P + $I(CH_2)_3OTMS$[3,4]	$I(CH_2)_3OH$	45

[1] A catalytic amount of p-toluenesulfonic acid was used.
[2] In the presence of PPTS as catalyst.
[3] Addition of solid potassium carbonate to the reaction mixture led to identical results.
[4] In the presence of solvents (benzene, acetonitrile) only unchanged starting materials were recovered.

From the mixture of dienols 7 and 8 obtained above, isomerically pure 7 >99% was achieved by careful column chromatography on silica gel, eluting with hexane-ethyl acetate mixtures. Acetylation of dienol 7 under standard conditions (acetic anhydride/pyridine) furnished the desired (3Z,5Z)-5-fluorotetradecadien-1-yl acetate 1 in 83% yield.

The reported procedure for the preparation of the fluorinated analog 1 could obviously be extended to the synthesis of the natural pheromone 2, since the fluorine atom effect on the stereochemistry of similar Wittig reactions has been proved to be negligible.[2] The procedure outlined above is specially of interest since the mixture of Z,E:E,E isomers of the natural attractant 2 in a 2:1 ratio is one of the most efficient attractive baits found in field tests,[1,12] being even better than the stereomerically pure Z,E isomer.

EXPERIMENTAL

Elemental analyses were obtained on a Carlo Erba 1106. Infrared spectra were determined on a Perkin Elmer spectrometer model 257. ^1H NMR spectra were recorded on a Bruker WP80SY or on a Varian XL200 spectrometers operating at 80 and 200 MHz respectively. ^{13}C and ^{19}F NMR spectra were obtained on a Bruker WP80SY at 20.15 and 75.39 MHz, respectively. Chemical shifts in ^1H and ^{13}C NMR spectra are reported in δ scale relative to TMS. In ^{19}F NMR spectra trifluoroacetic acid was used as external standard. GLC analyses were performed on a Carlo Erba 4130, using a fused silica capillary column SE-54 50m x 0.32 mm i.d. with H_2 as carrier gas.

All solvents were freshly distilled before use. THF and ether were distilled from Na/benzophenone. Anhydrous CCl_4 was prepared by distillation over P_2O_5 and anhydrous pyridine by distillation over KOH.

3-Hydroxypropyltriphenylphosphonium chloride 5.

Compound 5 was prepared according to the literature.[13]

^{1}H NMR 80 MHz ($CDCl_3$) δ 2.1-1.4 (b, 2H, CCH_2C), 3.77 (c, 4H, CH_2P and CH_2O), 4.25 (s, 1H, OH), 7.68 (c, 15H, aromatic protons).

^{13}C NMR 20 MHz ($CDCl_3$) 19.6 (d $^1J_{CP}$=52.7 Hz, C-1), 25.7 (d $^2J_{CP}$=4.0 Hz, C-2), 60.1 (d $^3J_{CP}$=16.4 Hz, C-3), 118.2 (d $^1J_{CP}$=85.4 Hz, 3C-ipso), 133.2 (d $^2J_{CP}$=9.4 Hz, 6C-ortho), 130.3 (d $^3J_{CP}$=13.4 Hz, 6C-meta), 134.8 (d $^4J_{CP}$=2.5 Hz, 3C-para).

5,5-Dimethyl-4,6-dioxaoctyltriphenylphosphonium chloride 6.

In a 25 ml distilling flask was placed 3.9 g (80 mmole) of 3-ethoxycrotonic acid and heated to 160ºC.[9] On sublimation, the acid decarboxylates to furnish 2-ethoxyprop-1-ene, which was collected over a mixture of 1.78 g (5 mmole) of 3-hydroxypropyltriphenylphosphonium chloride 5, 60 mg of PPTS and 150 ml of anhydrous $CHCl_3$, previously cooled to -20ºC. When the distillation was complete, the mixture was stirred at this temperature for 15 min. After this period of time, 5.5 ml of anhydrous Et_3N was added and the reaction mixture further stirred for 10 min. The solvents were removed under vacuum and the residue washed with anhydrous ether and decanted to yield 2.2 g (100%) of compound 6, which was dried under vacuum (0.1 Torr). Due to its highly hygroscopic character, the salt has been characterized only by its IR and ^{1}H NMR spectroscopic properties.

IR ($CHCl_3$) ν 2980, 2910, 1430, 1110 cm.$^{-1}$

^{1}H NMR 80 MHz ($CDCl_3$) δ 1.05 (t J=7.3 Hz, 3H, CH_2CH_3), 1.25 (s, 6H, $C(CH_3)_2$), 1.90 (c, 2H, $CH_2CH_2CH_2$), 3.35 (q J=7.3 Hz, 2H, OCH_2CH_3), 3.62 (t J=6.2 Hz, 2H, OCH_2CH_2), 3.82 (c, 2H, CH_2P), 7.5-8.10 (c, 15H, aromatic protons).

(3Z,5Z)-5-Fluorotetradecadien-1-ol 7.

In a 100 ml three-neck round bottomed flask, equipped with a magnetic stirring bar, gas inlet, calcium chloride tube and serum cap, was placed 2 g (4.5 mmole) of phosphonium salt 6 dissolved in a mixture of 40 ml of anhydrous THF and 8 ml of anhydrous HMPT. To the reaction system, cooled to -70ºC, was added, dropwise under nitrogen, 5.6 ml of a 0.8M soln. of n-BuLi in hexane (4.5 mmole). After 45 min. of stirring, 0.245 g (1.45 mmole) of (Z)-2-fluoro-2-undecenal 4[4] was added and the mixture stirred 1 h at -70ºC and 19 h at room temperature. The reaction mixture was quenched by pouring into ice-water and extracted repeatedly with hexane. The combined organic extracts were washed with brine and dried ($MgSO_4$) to yield, after stripping off the solvent, the expected mixture of (3Z,5Z) and (3E,5Z)-5-fluorotetradecadien-1-ols 7 and 8, in a 2:1 isomer ratio, as an oil.

Purification of the crude by column chromatography on Florisil, eluting with a mixture of hexane:ethyl acetate 95:5, afforded the following joined fractions.

1. First fraction (50 mg, 15%) of (Z,Z)-7 100% isomerically pure, according to GLC analysis on a fused silica capillary column (SE-54, 50 m x 0.32 mm i.d.).
2. Second fraction (100 mg, 30%) of a mixture of dienols 7 and 8 70:30 on GLC analysis.
3. Third fraction (42 mg, 13%) of a mixture of dienols 7 and 8 50:50 on GLC analysis.

From the second fraction, additional 29 mg of 7 100% isomerically pure was obtained after purification by column chromatography on 10% $AgNO_3$ impregnated silica gel.

IR (CCl_4) (Second fraction) ν 3350, 2930, 2865, 1655, 1615, 1210, 905 cm.$^{-1}$

^{1}H NMR 200 MHz ($CDCl_3$) (3Z,5Z)-7 δ 0.88 (t J=6.8 Hz, 3H, CH_2CH_3), 1.10-1.80 (c, 12H, CH_3CH_2 and $CH_2CH_2CH_2$), 2.12 (c, 2H, $CH=CHCH_2$), 2.64 (q J=6.4 Hz, 2H, $CF=CHCH_2$), 3.69 (c, 3H, CH_2OH), 4.79 (dt J=36.46 and 7.69 Hz, 1H, CH=CF), 5.44 (dt J=12.06 and 7.9 Hz, 1H, $CH=CHCH_2$), 5.78 (ddt J=30.5, 12.06 and 1.52 Hz, 1H, CFCH=CH).

^{1}H NMR 200 MHz ($CDCl_3$) (3E,5Z)-8 δ 0.81 (t J=6.5 Hz, 3H, CH_2CH_3), 1.10-1.70 (c, 12H, CH_3CH_2 and $CH_2CH_2CH_2$), 2.10 (c, 2H, $CH=CHCH_2$), 2.38 (q J=6.3 Hz, 2H, $CF=CHCH_2$), 3.60 (t J=6.8 Hz, 2H, CH_2OH), 4.63 (dt J=36.66 and 7.62 Hz, 1H, CH=CF), 5.73-5.91 (c, 2H, CFCH=CH).

^{13}C NMR 20 MHz ($CDCl_3$) (3Z,5Z)-7 62.5 (C-1), 32.6 (C-2), 127.6 (C-3), 122.9 (C-4), 156.4 (C-5), 112.3 (C-6), 23.9 (C-7), 29.1-29.2 (C-8 to C-11), 31.8 (C-12), 22.5 (C-13), 13.9 (C-14).

^{13}C NMR 20 MHz ($CDCl_3$) (3E,5Z)-8 61.9 (C-1), 35.8 (C-2),

125.8 (C-3), 125.1 (C-4), 155.6 (C-5), 109.7 (C-6), 24.1 (C-7), 29.3 (C-8 to C-11), 31.9 (C-12), 22.7 (C-13), 14.1 (C-14).

Elem. 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 1

To a solution of 50 mg (0.22 mmole) of (Z,Z)-7 100% isomerically pure in 2.2 ml of CCl_4 were added 0.8 ml of Ac_2O and 1 ml of anhydrous pyridine. The mixture was stirred at room temperature until no starting material remained by GLC analysis (3 h). Methanol was added and the solution stirred for 15 min. more. After evaporation of the solvents, the residue was taken up in CH_2Cl_2, washed with 2N HCl, $NaHCO_3$ sat. soln. and brine and dried ($MgSO_4$). Removal of the solvent furnished 52 mg (83%) of the expected (3Z,5Z)-5-fluorotetradecadien-1-yl acetate 1, which was purified by bulb-to-bulb distillation, b.p. 95-100ºC/0.05 Torr.

IR (CCl_4) ν 2935, 2865, 1740, 1260, 1230 cm^{-1}

^1H NMR 80 MHz ($CDCl_3$) (3Z,5Z)-1 δ 0.88 (t J=6.5 Hz, 3H, CH_2CH_3), 1.25 (b, 12H, CH_3CH_2 and $CH_2CH_2CH_2$), 2.1 (c, 5H, $CH=CHCH_2$ and $COCH_3$), 2.62 (c, 2H, $CF=CHCH_2$), 4.0 (t J=6.8 Hz, 2H, CH_2O), 4.8 (dt J=36.5 and 7.7 Hz, 1H, CH=CF), 5.4-5.6 (c, 1H, $CH=CHCH_2$), 5.7-6.1 (c, 1H, CFCH=CH).

^{19}F NMR 75.4 MHz ($CDCl_3$) (3Z,5Z)-1 -41.82 (dd J=36.01 and 27.96 Hz).

Elem. Anal. Calcd. for $C_{16}H_{27}FO_2$: C, 71.18; H, 10.08
Found: C, 71.01; H, 9.98.

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