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# SYNTHESIS OF (Z)-10,10-DIFLUORO-13-HEXADECEN-11-YNYL ACETATE, NEW DIFLUORO ANALOGUE OF THE SEX PHEROMONE OF THE PROCESSIONARY MOTH

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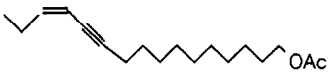
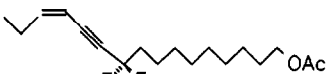
**Abstract.** *The synthesis of (Z)-10,10-difluoro-13-hexadecen-11-ynyl acetate* **2**, *a new difluorinated analogue of the sex pheromone of the pine processionary moth is reported. The synthesis is based on the radical addition reaction of difluoroiodoacetylene* **6** *to 8-nonenyl alcohol protected as TBDMS ether* **4** *or acetate* **5**. *Physicochemical features and biological activity of the compound are also compared with those of the natural pheromone.*

It is well known that the special features of the fluorine atom, i.e. steric volume similar to that of hydrogen, high electronegativity and high carbon-fluorine bond energy, lead to deep and unexpected changes in the activities of the organofluorinated molecules when compared with those of the non-fluorinated counterparts[1]. In insect sex pheromones, replacement of hydrogen atom(s) by fluorine has been shown by us and others to mimic, synergize or inhibit the action of the parent non-fluorinated molecules[2a-d].

The processionary moth *Thaumetopoea pityocampa* (Denis and Schiff.) (Lepidoptera, Thaumetopoeidae) is one of the most important pine pests in the Mediterranean countries. The major component of the sex pheromone was identified by us as (Z)-13-hexadecen-11-ynyl acetate[3] **1** and the synthetic material proved to be active in the field[4]. In this context and in connection with our ongoing project on the development of inhibitors of the pheromone action by competitive binding with the antennal receptors[5a-b], we now report on the synthesis of (Z)-10,10-difluoro-13-hexadecen-11-ynyl acetate **2**, a new difluorinated analogue of **1**. To our knowledge, compound **2** is the first difluoro derivative wherein a methylene group located in propargylic position to an enyne function is replaced by a difluoromethylene group[6a-c].




**1**

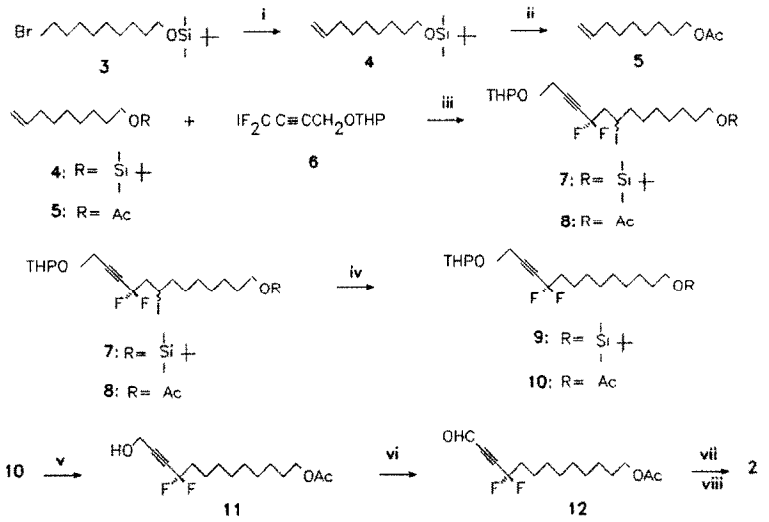



**2**

The synthesis is based on the AIBN-catalyzed addition reaction of THP-protected difluoroiodobutynol **6** to 8-nonenyl alcohol protected as TBDMS ether **4** or acetate **5**. Compound **5** was prepared by $FeCl_3$-catalyzed[7] acetylation reaction of **4**, which resulted from dehydrobromination of TBDMS-protected 9-bromononanol **3** with potassium *tert*-butoxide in THF. Difluorinated compound **6** was prepared from THP-protected propargyl alcohol, as previously described[6c].

Preliminary trials to obtain compound **9** by nucleophilic reaction of the lithium salt or Grignard derivative of **3** with **6** under a variety of conditions were unsuccessful. Alternatively, utilization of a mild radical reaction was considered. In this context, addition reactions of iodofluorinated compounds to alkenes have been described using a radical source[8a] or copper powder[8b] as catalysts. In our case, AIBN-catalyzed reactions of compounds **4** and **5** with **6** proceeded successfully to furnish compounds **7** and **8**, respectively, in good yields, without affecting the protecting group or the

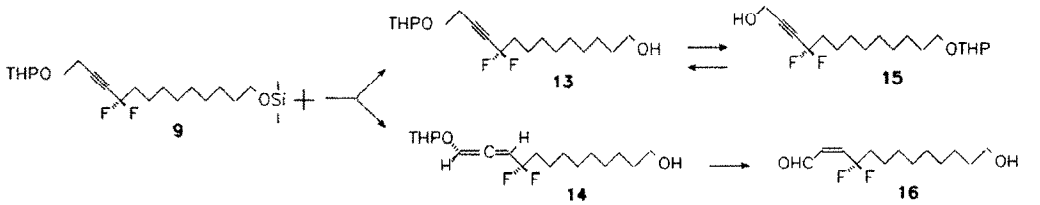
triple bond (Scheme 1). Deiodination of **7**, under non-acidic conditions to avoid THP hydrolysis, was initially tried with *n*-BuLi at -78°C[6a], but only a complex mixture of products was obtained. Consequently, a much milder dehalogenation conditions were needed and, again, a radical elimination reaction with organotin hydrides appeared to be attractive to us[9]. In fact, when compound **7** was allowed to react with $Bu_3SnH$, in the absence of solvent or catalyst, the desired deiodinated compound **9** was obtained in 80% yield with preservation of the fluorine atoms. The process was also successfully applied to acetate **8** to give rise to **10** in 68% yield, without concomitant reduction of the ester group. In both cases, no traces of the corresponding allenes were detected.




*i: t-BuOK/THF, 60°C, 58%; ii: $Ac_2O$, $FeCl_3$, 0°C, 73%; iii: AIBN/benzene, sealed tube,80°C, 68% for 7, 59% for 8; iv: $Bu_3SnH$, rt, 80% for 9, 68% for 10; v: PPTS/EtOH, 55°C, 67%; vi: $MnO_2/CHCl_3$, sealed tube 60°C, 6 days, 86%; vii: $Ph_3P$=CHEt/THF, -70°C, 34%.*

Scheme 1

When compound **9** was subjected to selective hydrolysis with tetrabutylammonium fluoride (3 equiv., room temperature, 4 hr) a mixture of the expected compound **13** and the allene **14**, in 60:40 ratio, was obtained in 80% yield, after purification on silica gel[10]. It is likely that the initial attack of the fluoride on the silicon atom leads to the intermediate formation of an alkoxide ion, which is basic enough to abstract one of the propargylic protons α to the THP group to give rise to the allene. In the presence of traces of acid and at room temperature, the alcohol **13** isomerized to **15** by transacetalization, whereas allene **14** yielded stereoselectively aldehyde **16** with *Z* configuration[11] (Scheme 2). These compounds were identified by their spectroscopic properties and confirmed through PANIC-85 spectra simulation program.




Scheme 2

Because of this unexpected difficulty, we shifted our attention to acetate **10**, from which no alkoxide species should be derived under hydrolysis conditions. In fact, selective hydrolysis of the THP ether in compound **10** was accomplished by reaction with pyridinium *p*-toluenesulfonate in ethanol at 55°C. It should be noted, however, that conventional acid treatment (*p*-TsOH acid) produced concomitant hydrolysis of the acetate group[12]. Oxidation of alcohol **11** to aldehyde **12** turned out to be troublesome since several oxidation agents (PDC in $CH_2Cl_2$, oxalyl chloride /DMSO), under a variety of conditions, lead directly to the acid. However, stirring alcohol **11** with active $MnO_2$ in $CHCl_3$ in a sealed tube at 60°C for 6 days, smoothly afforded aldehyde **12** in 86% yield[13]. Wittig reaction of the aldehyde with *n*-propyltriphenylphosphonium ylide unexpectedly yielded a *Z/E* mixture of the desired difluorinated enyne **2** along with variable amounts of 10,10-difluoro-11-dodecynyl acetate **17**, the formal decarbonylation product of aldehyde **12**. The same secondary product was obtained when the parent non-fluorinated aldehyde was used. Generation of the terminal acetylene was attributed to the presence of free base in the reaction medium when generation of the ylide was not complete. In fact, when aldehyde **12** was allowed to react with *n*-BuLi, in the absence of the phosphonium salt, only the acetylene **17** was formed.

In order to minimize the formation of **17**, several reaction conditions were tested to finally obtain a 5:1 ratio of (*Z/E*)-**2**:**17** in 41% yield, when the ylide was prepared at 0°C for 15 min and room temperature for 45 min, and the subsequent Wittig reaction carried out at -70°C for 1 h and room temperature for 1 h more. The reaction afforded **2** as a mixture of isomers *Z:E* 52:48, presumably due to an enhanced stability of the *threo* betaine, due to an intramolecular H...F bond, in comparison with the *erythro* betaine, wherein no hydrogen bonding is possible. Consequently, and albeit the reaction was performed under kinetic control, an unfavourable increase of the *E* isomer should result, as it is observed. This assumption, which would also imply an enhanced difficulty of extrusion of $Ph_3PO$, was supported by the fact that the non-fluorinated substrate gave, under similar conditions, the expected natural pheromone **1** in good yield (60-65%) and stereomeric purity (90-95% *Z*)[14,15]. Compound **2**, which was purified by semipreparative HPLC, exhibited higher volatility than the natural pheromone **1** (GC: $r_t$ 10.05 and 10.54 min., respectively, on a non-polar SPB-5 capillary column, and 12.29 and 11.18 min., respectively, on a highly polar Supelcowax 10 capillary column), and also higher polarity than the parent compound (TLC: $r_f$ 0.47 for **2** and 0.52 for **1** on silica gel in pentane:AcOEt 90:10; HPLC: $r_t$ 9.95 min. for **2** and 17.65 min. for **1** on Spherisorb ODS-2 15 x 1cm 5μm, MeOH:$H_2O$ 80:20).

Compound **2** was essentially inactive when tested in electroantennogram (EAG) assays and as an attractant in field trapping experiments. However, this compound produced a 24% reduction of the EAG response to the natural pheromone component when male moths were pre-exposed to vapors of the fluorinated analogue prior to the EAG assay. Similarly, in field tests difluorinated analogue **2** decreased the number of catches by 49% when mixed with **1** in a 1:1 ratio. Consequently, the profound electronic changes, and not the small difference in steric volume, induced by introduction of the fluorine atoms in α-position to the triple bond of the original pheromone molecule, has resulted in considerable loss of activity of the resulting compound **2**, which confirms the key role played by the enyne function in the natural pheromone.

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10. Selected spectroscopic features of allene **14** and aldehyde **16** are as follows. **14**: IR $\nu$ 1940 $cm^{-1}$, $^1H$ NMR (80 MHz) $\delta$ 5.95 (m, 1H, =C=CHCF$_2$), 6.90 (m, 1H, THPOCH=C=), 4.95 (t J=3.0 Hz, 1H, OCHO). $^{19}F$ NMR $\delta$ -13.9 (dt, J=J'=15.4 Hz). **16**: IR $\nu$ 1695 $cm^{-1}$, $^1H$ NMR (80 MHz) $\delta$ 10.15 (dm J=7.3 Hz, 1H, CHO), 6.18 (m, 1H, =C<u>H</u>CHO), 6.55 (m, 1H, CF$_2$CH=C), 4.58 (t J=3.0 Hz, 1H, OCHO). $^{19}F$ NMR $\delta$ -13.9 (dt, J=J'=14.7 Hz)
11. A similar but non-stereoselective process of conversion of a non-fluorinated allene into the corresponding $\alpha,\beta$-unsaturated aldehyde has been described: E.J. Corey, Sh. Terashima, *Tetrahedron Lett.* 1972, 1815-6.
12. Spectroscopic data of **11**: IR $\nu$ 3605, 3405, 2255, 1727 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 4.37 (t J=4.2 Hz, 2H, CH$_2$OH), 4.05 (t J=6.9 Hz, 2H, CH$_2$OAc), 2.05 (s, 3H, CH$_3$CO), 2.10-1.93 (c, 2H, CH$_2$CF$_2$), 1.68-1.48 (c, 4H, C<u>H</u>$_2$CH$_2$CF$_2$, C<u>H</u>$_2$CH$_2$OAc), 1.31 (b, 10H, 5CH$_2$), 1.80 (b, 1H, OH). $^{13}C$ NMR $\delta$ 171.36 (CO), 114.72 (t J= 230.8 Hz, C-10), 84.92 (t J=6.9 Hz, C-12), 78.77 (t J=41.4 Hz, C-11), 64.62 (C-13), 50.60 (C-1), 39.07 (t J=25.5 Hz, C-9), 29.20-28.53 (C-2 and C-4 to C-7), 25.81 (C-3), 22.66 (t J=3.3 Hz, C-8), 21.06 (<u>C</u>H$_3$CO). $^{19}F$ NMR $\delta$ -7.25 (tt J=14.9 Hz, J'=4.2 Hz).
13. Spectroscopic data of **12**: IR $\nu$ 1720, 1672 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 9.30 (t J=1.2 Hz, 1H, CHO), 4.05 (t J=6.9 Hz, 2H, CH$_2$OAc), 2.10 (m, 2H, CH$_2$CF$_2$), 2.05 (s, 3H, CH$_3$CO), 1.70-1.45 (c, 4H, C<u>H</u>$_2$CH$_2$O, C<u>H</u>$_2$CH$_2$CF$_2$), 1.31 (b, 10H, 5CH$_2$). $^{13}C$ NMR $\delta$ 175.14 (t J=1.9 Hz, HCO), 171.28 (<u>C</u>OCH$_3$), 114.37 (t J=234.5 Hz, C-10), 84.57 (t J=42.5, C-11), 81.99 (t J=6.3 Hz, C-12), 64.60 (C-1), 38.63 (t J=24.6 Hz, C-9), 29.3-28.5 (C-2 and C-4 to C-7), 25.8 (C-3), 22.37 (t J=3.5 Hz, C-8), 21.05 (C-1'). $^{19}F$ NMR $\delta$ -10.40 (dt J=15.3 Hz, J'=1.2 Hz).
14. Spectroscopic data of **2**: IR $\nu$ 2215, 1735 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 6.11 (dtt J=10.9 Hz, J'=7.5 Hz, J''=0.9 Hz, 1H, CH$_2$C<u>H</u>=C), 5.47 (dtt J=10.9 Hz, J'=4 Hz, J''=1.5 Hz, 1H, =CH-C ), 4.05 (t J=6.9 Hz, 2H, CH$_2$OAc), 2.33 (dq, J=J'=7.5 Hz, 2H, C<u>H</u>$_2$CH=), 2.05 (s, 3H, CH$_3$CO), 2.12-1.97 (c, 2H, C<u>H</u>$_2$CF$_2$), 1.66-1.50 (c, 4H, C<u>H</u>$_2$CH$_2$CF$_2$, C<u>H</u>$_2$CH$_2$OAc), 1.42-1.24 (b, 10H, 5CH$_2$), 1.04 (t J=7.5 Hz, 3H, C<u>H</u>$_3$CH$_2$CH=). $^{13}C$ NMR $\delta$ 171.2 (CO), 149.6 (t J=3.2 Hz, C-14), 115.5 (t J=230 Hz, C-10), 106.2 (t J=3.3 Hz, C-13), 85.8 (t J=40.1 Hz, C-11), 83.4 (t J=6.9 Hz, C-12), 64.6 (C-1), 39.4 (t J=26.0 Hz, C-9), 29.3-28.6 (C-2 and C-4 to C-7), 25.9 (C-3), 24.0 (C-15), 22.9 (t J=3.3 Hz, C-8), 21.0 (C-1'), 13.2 (C-16). $^{19}F$ NMR $\delta$ -5.83 (dt J=14.6 Hz, J'=3.9 Hz). Exact mass for $C_{18}H_{27}FO_2$ (M-HF)$^+$: 294.1977; calculated: 294.1995.
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