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Fluorinated Analogs of Ester Components of Red Bollworm Sex Pheromone

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FLUORINATED ANALOGS OF ESTER COMPONENTS OF RED BOLLWORM SEX PHEROMONE

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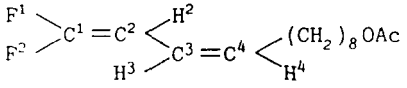
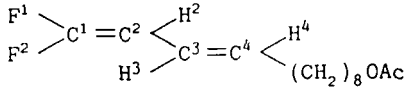
Abstract: *Fluorinated analogs of the two geometrical isomers of the red bollworm moth sex pheromone were synthetized by palladium-catalyzed cross coupling reactions.*

The red bollworm moth, *Diparopsis castanea*, is a major cotton pest in South-Eastern Africa (1). The main component of the physiologically active mixture of compounds isolated from female abdominal tips is the 9,11-dodecadien-1-yl acetate (E/Z=80/20) (2).
Recently, incorporation of fluorine into bioactive molecules has been studied by several laboratories. Hydrogen can be replaced by fluorine without notable steric consequences and it seemed possible that fluoroanalogs of pheromones might show interesting biological activities (3-5).
In this present publication, is reported the synthesis of two 1,1-difluorinated 10 and 11 in which terminal hydrogens have been replaced by fluorine atoms.



10



11

2,2-difluorovinyllithium reagent (6) has been shown to have a restricted thermal stability. Nevertheless, we have reported that organozinc derivative was very stable and could react with vinylic halides under palladium catalysis. The preparation of various 1,1-difluorodienes with aliphatic chain, has been described in a

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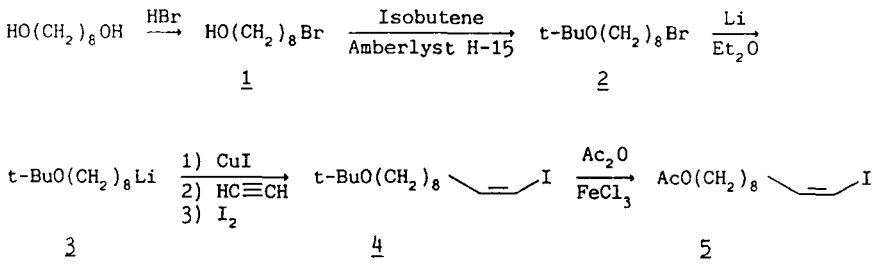
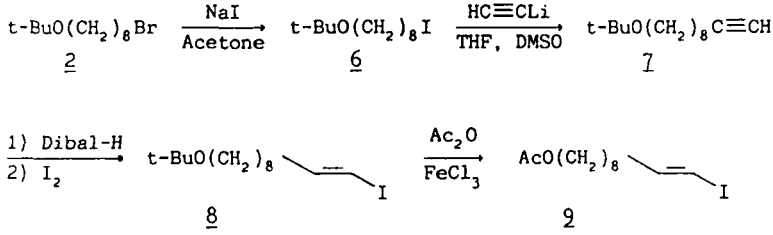
previous paper (7,8). Herein, we have applied this stereoselective coupling reaction between 2,2-difluorovinylzinc bromide and vinylic iodide (Z) or (E) to the synthesis of functionalized dienes. The pure (Z) alkenyl synthon was obtained by carbocupration of acetylene according to Normant et al (9) and the pure (E) by hyroalumination with diisobutylaluminium hydride of the appropriate alkyne (10). The alcohol was first protected as t-butyl ether because in two recent publications (11), Alexakis et al have pointed out the great advantages of this protective group: The preparation and the reactivity of ω-terbutoxy Grignard reagents were exactly as the non-functionalized ones and in contrast to classical protected ω-hydroxyalkyne, ω-terbutoxyalkyne underwent smooth hydroalumination.
The syntheses of fluorodienes 10 and 11 are illustrated by the following schemes:



The bromohydrin 1 (prepared according to the usual procedure) was protected as t-butyl ether by reaction with isobutene and an acid catalyst. The ω-terbutoxy organolithium derivative 3 was prepared in Et_2O in good yield and reacted successively with CuI and acetylene to give the corresponding vinylcuprate which led to product 4 after iodolysis in a good yield and with an isomeric purity ⩾99%.



The bromohydrin 2 was converted into the iodide 6 which was alkylated with lithium acetylide. The resulting alkyne 7 was hydroaluminated with DIBAL-H and the intermediate alkenyl alane was iodinated *in situ* leading to the (E) iodide 8 in a good yield and steric purity ⩾99%. The t-butyl ether 4 and 8 were easily

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cleaved into the corresponding acetates 5 and 9 under mild conditions without isomerisation.

The difluorovinylzinc bromide, prepared *in situ* from difluoroethylene and s-Buli following by a transmetalation, was successively coupled with alkenyl iodides 5 and 9 in presence of Pd° catalyst to afford respectively the dienes 10 and 11 in good yields. This coupling reaction occurs with retention of configuration.

$$CF_2{=}CH_2 \xrightarrow[-\ 100^{\circ}C]{\text{s-BuLi}} \left[CF_2{=}CHLi \xrightarrow[-\ 100^{\circ}C]{ZnBr_2} CF_2{=}CHZnBr \right] \xrightarrow[Pd^{\circ}]{RCH{=}CHI}$$

(R = $(CH_2)_8OAc$)

$CF_2{=}CH{-}CH{=}CHR$ 10 : 82% from 5
11 : 75% from 9

In conclusion, this route allowed to prepare products of very high stereoisomeric purities in excellent overall yields. Both isomers (E) and (Z) are now available for laboratory and fields bioassays.

Experimental section

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Brucker AC 200 and a Jeol FX 90Q spectrometers ($CDCl_3$; δ (ppm) from TMS, J(Hz)). Mass spectra were obtained by using a Nermag R10X10. Infrared spectra were measured on a Perkin Elmer 397 spectrometer (neat, cm^{-1})). Gas chromatographic analyses were performed on a model 2900 Carlo Erba instrument equipped with fused silica capillary polar columns (25 m WCOT FFAP 0.32 id, 0.3 μm phase).

8-bromo-1-octanol 1

A stirred mixture of 1,8-octanediol 92 g (0.63 mol), 360 ml of 48% aqueous HBr and 120 ml water was heated at 80°C while continuously extracted by cyclohexane. After one day the cyclohexane solution was cooled, the precipitate of diol was filtered off and the filtrate was concentrated *in vacuo*. The remainding aqueous mixture was again heated and continuously extracted by cyclohexane. This operation was repeated on five days after which a total of 105.3 g (80% crude yield) of 1 was obtained.

8-bromo-1-terbutoxyoctane 2

Isobutene was bubbled into a stirred mixture of 104.5 g (0.5 mol) of bromoalcohol 1, 250 ml of hexane and 12.5 g of Amberlyst H-15 at room temperature for 8 h. After filtration, the solvent was evaporated and the residue distilled over $NaHCO_3$ to yield 125.9 g of 2 (95% yield). Bp.90°C/0.01 Torr. m/z: M-15 (249 ^{79}Br, 251 ^{81}Br).

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10-iodo-1-terbutoxy-9-decene 4

100 ml (0.1 mol) of an etheral solution (1N) of lithium reagent 3 (prepared from 39.7 g (0.15 mol) of 2 and 2.5 g of lithium) were added to a stirred suspension of cuprous iodide 9.9 g (0.052 mol) in 100 ml Et_2O at -50°C. The stirring was maintained for 30 min at -35°C. Acetylene 2.5 l (0.11 mol) was bubbled into this blue solution at -55°C and after 30 min at -25°C, a greenish solution of (Z) 1-vinyl cuprate was obtained. To this reagent were added at -60°C, 25.4 g (0.1 mol) of iodine and the stirred mixture was warmed to -15°C until discolouration. The mixture was hydrolyzed with NH_4OH+NH_4Cl aq. sat. solution, admixed with pentane (100 ml), filtered and extracted with Et_2O. The organic phase was washed successively with $Na_2S_2O_3$, $NaHCO_3$ and NH_4Cl sat. aq. solutions. It was then dried over $MgSO_4$ and concentrated on a rotatory evaporator. The residue was distilled over Cu powder to afford 16.9 g of iodide 4 (50% yield) with isomeric purity ≥99%. Bp.115°C/0.1 Torr. IR: 1600 (HC=CH), 1190 (C-O). ^1H NMR: 1.15 (s,9H) CH_3, 1.3-1.5 (m,12H) CH_2, 2.1 (m,2H) $CH_2CH=$, 3.3 (t,2H) CH_2O, 6.15 (m,2H) HC=CH. ^{13}C NMR: 34.6 ($CH_2CH=$), 61.5 (CH_2O), 72.2 (C-O), 82.0 (=CHI), 141.3 (CH=).

8-iodo-1-terbutoxyoctane 6

A mixture of 53 g (0.2 mol) of 2, 66 g (0.44 mol) of NaI and acetone (150 ml) was refluxed for 48 h. 200 ml of pentane were added in order to precipitate the mineral salts which were filtered off. The filtrate was concentrated *in vacuo* and the residue was distilled to yield 58 g of 6 (93% yield). Bp.110°C/0.1 Torr. m/z: 297 (M-15).

1-terbutoxy-9-decyne 7

Acetylene was bubbled into 250 ml of THF at -20°C until saturation. To this solution were added 125 ml (0.2 mol) of n-BuLi (1.6M) in hexane at -80°C then DMSO (100 ml) and slowly 46.8 g (0.15 mol) of iodide 6 at -70°C. The mixture was stirred overnight at room temperature, hydrolyzed with H_2SO_4 solution (1N) and extracted with Et_2O.. The organic phase was washed 3 times with water, in order to remove the DMSO, $NaHCO_3$ and NaCl sat. aq. solutions, then dried over $MgSO_4$. The solvents were evaporated and the residue distilled affording 27.7 g of alkyne 7 (88% yield). Bp.70°C/0.1 Torr. m/z: 195 (M-15). IR: 3300 and 2100 (C≡C) , 1190 (C-O). ^1H NMR: 1.15 (s,9H) CH_3, 1.4 (m,12H) CH_2, 1.9 (t,1H) CH≡, 2.1 (m,2H) $CH_2C\equiv$, 3.3 (t,2H) CH_2O. ^{13}C NMR: 18.4 ($CH_2C\equiv$), 61.5 (CH_2O), 68.3 (CH≡), 72.3 (C-O),84.35 (C≡).

(E)-10-iodo-1-terbutoxy-9-decene 8

To a solution of alkyne 7, 21 g (0.1 mol), in 20 ml of anhydrous hexane, were added dropwise 100 ml (0.1 mol) of (1M) diisobutylaluminium hydride solution in hexane at room temperature. The reaction mixture was stirred at 50°C for 4 h, then cooled to -70°C. 50 ml of THF followed by iodine 25.4 g (0.1 mol) in 50 ml of THF were added. The stirred mixture was allowed to warm up to room temperature for 1 h, cooled again to -50°C, hydrolyzed with H_2SO_4 solution (1N) and extracted with Et_2O. The organic phase was washed successively with $Na_2S_2O_3$, $NaHCO_3$ and

NaCl sat. aq. solutions. It was then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled over Cu powder to afford 23.7 g of 8 (70% yield). Bp.115°C/0.1 Torr. (E) purity (≥99%). m/z: 323 (M-15). IR: 1600 (HC=CH), 1190 (C-O), 940 (HC=CH) trans. ^{1}HNMR: 1.15 (s,9H) CH_3, 1.4 (m,12H) CH_2, 2.05 (m,2H) CH_2CH=, 3.3 (t,2H) CH_2O, 5.9 (d,1H) ICH=, 6.4 (dt,1H) HC=, (J=14 and 7). ^{13}C NMR: 36.0 (CH_2CH=), 61.4 (CH_2O), 72.1 (C-O), 74.3 (ICH=), 146.4 (HC=).

Note: This product contained two impurities: (1) $tBuO(CH_2)_8C{\equiv}CI$, this iodoalkyne could be removed by treatment with 20% of HeptCu (HeptLi + CuI in Et_2O (-40°C/30 min) then THF) for 2h at -40°C ($tBuO(CH_2)_8C{\equiv}CHept$ was obtained and removed by distillation). (2) $tBuO(CH_2)_{10}I$, this iodoalkane was removed by treatment with n-butylamine (12).

(Z)-1-acetoxy-10-iodo-9-decene 5 and (E)-1-acetoxy-10-iodo-9-decene 9

9.4 ml (0.1 mol) of Ac_2O and 0.8 g (0.005 mol) of $FeCl_3$ were added successively to a solution of t-butyl ether 4 or 8, 16.9 g (0.05 mol) in Et_2O (100ml). The solution was stirred at room temperature overnight. A sat. aq. solution of $NaHPO_4$ was added and the mixture was stirred for 1 h. The solid $FePO_4$ precipitate was filtered off. After usual work up, 15.2 g of acetate 5 or 9 were obtained (94% yield).

5: Bp.112°C/0.1 Torr. (Z) purity (≥99%). IR: 1730 (C=O), 1600 (HC=CH), 1235 (C-O). ^{1}H NMR: 1.3-1.6 (m,12H) CH_2, 2.05 (s,3H) CH_3CO, 2.1 (m,2H) CH_2CH=, 4.0 (t,2H) CH_2O, 6.17 (m,2H) HC=CH. ^{13}C NMR: 34.6 (CH_2CH=), 64.3 (CH_2O), 82.4 (=CHI), 141.1 (CH=), 170.3 (C=O).

9: Bp.110°C/0.1 Torr. (E) purity (≥99%). IR: 1730 (C=O), 1595 (HC=CH), 1235 (C-O), 945 (HC=CH) trans. ^{1}H NMR: 1.3 (m,12H) CH_2, 2.0 (m,5H) CH_2CH= and CH_3CO, 4.05 (t,2H) CH_2O, 5.96 (d,1H) ICH=, 6.51 (dt,1H) CH= (J=14.4 and 7). ^{13}C NMR: 36.0 (CH_2CH=), 64.3 (CH_2O), 74.5 (=CHI), 146.4 (CH=), 170.4 (C=O).

(Z)-12,12-difluoro-9,11-dodecadien-1-yl acetate 10 and (E)-12,12-difluoro-9,11-dodecadien-1-yl acetate 11

To solution of 1,1-difluoroethylene, 3.8 g (0.06 mol) in THF (80 ml) and Et_2O (20ml) were added at -100°C, 0.05 mol of s-BuLi in cyclohexane. The reaction mixture was stirred at -90°C for 20 min, and at -100°C was added an anhydrous $ZnBr_2$ solution (12.4 g (0.055 mol)/50ml THF). The stirring was maintained for 20 min at -90°C and 1,1-difluorovinylzinc bromide was obtained. To this reagent were added successively at 0°C a solution of $Pd(PPh_3)_4$ (2%) (0.46g/20ml THF) and 30 mmol of the desired vinylic iodide 5 or 9. The stirred solution was allowed to reach room temperature and after 30 min for 9 or 90 min for 5, it was hydrolyzed by H_2SO_4 solution (1N). After usual work up, cyclohexane was added to the crude and the salts were filtered on silica gel. The solvent was removed and the residue was distilled to afford the product 10 or 11.

10: Bp.86-87°C/0.1 Torr. (Z) purity (≥99%). IR: 1740, 1710 (CF_2=CH

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and C=O), 1630 (HC=CH). ^{19}F NMR ($C_6H_5CF_3$): -24.2 (dd,F^2) $J(F^2F^1)$=29, $J(F^2H^2)$=23, -25.1 (d,F^1) $J(F^1H^2)\simeq 0$. ^1H NMR: 1.3 (m,10H) CH_2, 1.6 (m,2H) CH_2, 2.0 (s,3H) CH_3CO, 2.05 (q,2H) CH_2CH=, 4.05 (t,2H) CH_2O, 5.14 (dddd,1H) H^2 $J(H^2F^2)$=24.0, $J(H^2H^3)$=11.4, $J(H^2F^1)$=2.3, $J(H^2H^4)$=1.1, 5.40 (dtm,1H) H^4 $J(H^4H^3)$=11.2, $J(H^4-CH_2)$=7.0, 5.85 (ddq,1H) H^3 $J(H^3H^2)$=11.4, $J(H^3H^4)$=11.2, $J(H^3F^1)$, $J(H^3F^2)$ and $J(H^3-CH_2)\simeq$1.3-1.4. ^{13}C NMR: 20.9, 26.1, 27.8, 28.8, 29.3, 29.4, 29.6, 64.6 (CH_2O), 78.2 (dd,C^2) $J(C^2F)$=26.2 and 16.8, 117.1 (dd,C^4) $J(C^4F)$=4.0 and 1.3, 132.0 (dd,C^3) $J(C^3F)$=11.1 and 3.7, 157.1 (dd,C^1) $J(C^1F)$=296.1 and 290.0, 171.0 (C=O).

11: Bp.83°C/0.03 TOrr. (E) purity (>99%). IR: 1740, 1720 (CF_2=CH and C=O), 1640 (HC=CH). ^{19}F NMR: -25.4 (dd,F^2) $J(F^2F^1)$=36, $J(F^2H^2)$=24.4, -28.1 (d,F^1) $J(F^1H^2)\simeq 0$. ^1H NMR: 1.3 (m,10H) CH_2, 1.6 (m,2H) CH_2, 2.02 (d,3H) CH_3CO, 2.05 (q,2H) CH_2CH=, 4.05 (t,2H) CH_2O, 4.9 (ddd,1H) H^2 $J(H^2F^2)$=24.6, $J(H^2H^3)$=10.6, $J(H^2F^1)$=1.8, 5.6 (dt,1H) H^4 $J(H^4H^3)$=15.5, $J(H^4-CH_2)$=6.8, 5.9 (ddq,1H) H^3 $J(H^3H^4)$=15.5, $J(H^3H^2)$=10.6, $J(H^3-CH_2)$=1.3, $J(H^3F^1)$ and $J(H^3F^2)$ 1.2 -1.3. ^{13}C NMR: 20.8, 26.2, 28.9, 29.3, 29.4, 29.6, 33.0, 64.6 (CH_2O), 82.2 (dd,C^2) $J(C^2F)$=26.2 and 17.5, 118.8 (dd,C^4) $J(C^4F)$=4.0 and 1.3, 133.5 (dd,C^3) $J(C^3F)$=11.1 and 3.0, 156.1 (dd,C^1) $J(C^1F)$=294.4 and 288.4, 170.9 (C=O).

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