Synthesis and Biological Activity of Point-Fluorinated Pheromone Analogues of *Eldana saccharina*

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Substitution of fluorine atoms on an organic molecule makes it possible to modify the molecular orbital and electron density of the surface without changing its molecular shape. Point-fluorinated analogues of the sex pheromone of the male African sugarcane borer were synthesized in optically active forms and their pheromone activities were investigated using an EAG test. The EAG activity of these point-fluorinated pheromone analogues indicates that the point of fluorination has a critical influence on the pheromone activity.

Introduction

Partly fluorinating analogues of biologically important compounds causes distinctive modifications in the activities of these compounds.[1−3] Fluorine atoms closely mimic the steric requirements of hydrogen atoms at enzyme receptor sites, but their strong electronegativity significantly alters the reactivity of neighboring centers. In addition, fluorine substitution increases lipid solubility, and enhances the rates of absorption and transport of the fluorinated derivatives. Therefore, fluorinated derivatives have been a subject of common interest to many groups, particularly in the field of pheromone chemistry, because of these special features of the fluorine atom.[2−4] Recently, we reported the synthesis of both enantiomers of α ,α-difluorinated analogues of eldanolide (+)-**1**,[5,6] which is a sex pheromone of the male African sugarcane borer, *Eldana saccharina*,[7] using a radical cyclization protocol.[5,6,8] It has been shown that substitutions in the polar group of lepidoptera pheromone molecules result in reduced recognition by the olfactory receptors[9] and produce potent inhibitors of the pheromone-catabolizing enzymes present in the olfactory tissues.[10] Therefore, we assumed that 2,2-difluoroeldanolides **2** would lose their pheromone activity, because α,α-difluoro-γ-lactone was believed to correspond to a cyclic carbonate rather than to the γ-lactone in vivo.[1] An electroantennogram (EAG) investigation,[10,11] however, of these pheromone analogues **2** revealed that both the (+)-**2** and (−)-**2** enantiomers were as active as the natural eldanolide (+)-**1** toward the insect olfactory receptors.[5] The binding property of a pheromone molecule with a receptor protein has been discussed based on its size and electronic interaction with a specific part of the protein and has been discussed from the standpoint of hydrogen bonding or coulomb energy; the docking of an agonist at a receptor site has been evaluated in terms of, for example, steric repulsion, van der Waals attraction, electrostatic forces, hydrogen bonds, and metal complexation.[2,12] Schlosser and co-workers were the first to synthesize a fluorinated analogue of an insect pheromone.[4] They carefully investigated the fluorine-modulated bioactivity in olfactory response and concluded that it can be rationalized without steric factors.[3] The origin, however, of molecular recognition of the olfactory molecule on the receptor protein is still obscure. Mori established that there exist many kinds of relationships between the stereochemistry of pheromones and their bioactivity.[13] He showed that there are at least ten categories of stereochemistry−pheromone activity relationships.[13] Although it has been pointed out that this complex relationship may be responsible for the inhibitory action of the antipode toward a pheromone-catabolizing enzyme,[9a] no answer to this matter has been proposed so far from the standpoint of molecular recognition on the pheromone receptor protein. An electrostatic potential map of natural eldanolide (+)-**1** and 2,2-difluoroeldanolide **2** indicates that

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these isomers look completely dissimilar (Figure 1), while the results of computational chemistry suggest that the shape of the two molecules are quite similar (Figure 1).[15]

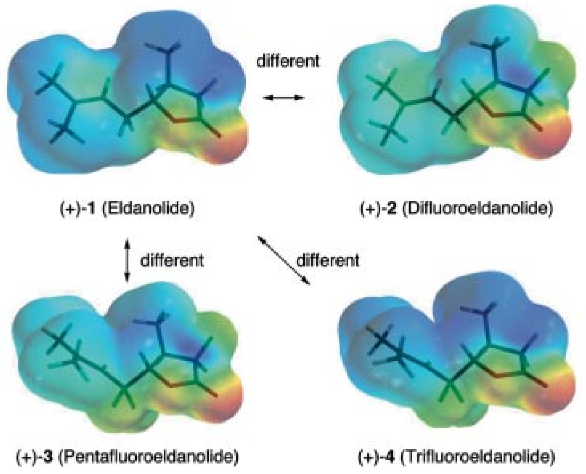
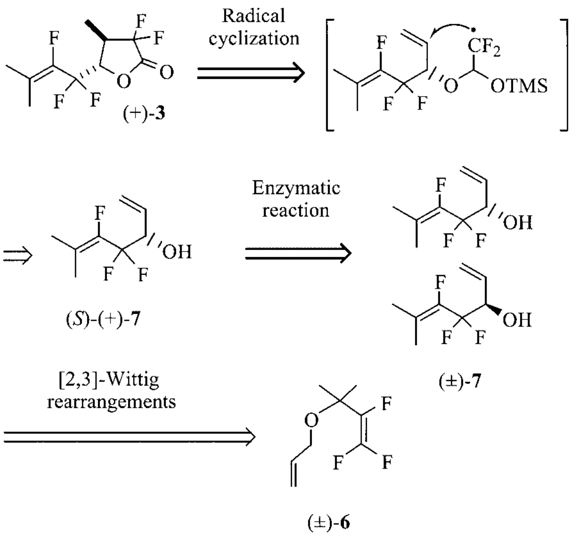


Figure 1. Electrostatic potential maps of eldanolide and fluorinated analogues by MO (PM3) calculations

Modification of the electron spin density at a specific part of a molecule is expected to occur by introduction of a fluorine atom instead of a hydrogen atom, as is shown in Figure 1. To gain more detailed insight into the molecular recognition of a pheromone molecule on the receptor protein, 5,5,6-trifluoroeldanolide [(+)-**3** and (−)-**3**] and 2,2,5,5,6-pentafluoroeldanolide [(+)-**4** and (−)-**4**] were chosen as the synthetic targets for the present study (Figure 1). These fluorinated-analogues **3** and **4** have a different pattern of electron spin density on their molecular surface from that of natural eldanolide **1** and 2,2-difluoroeldanolide **2**. Here, we report the full details of the synthesis of the partly fluorinated eldanolides **3** and **4**[8] in optically active forms, and the results of EAG tests of these novel pheromone analogues.

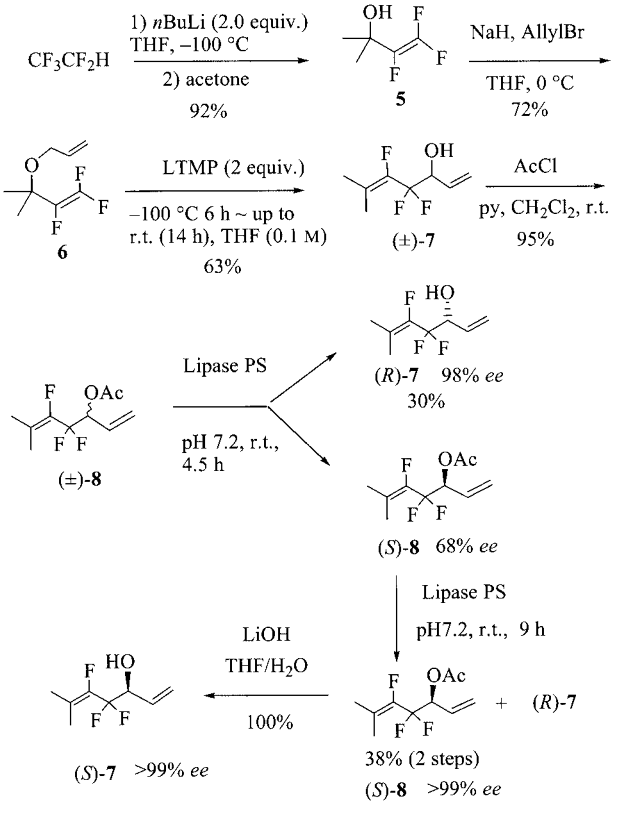


Scheme 1. Retrosynthetic analysis of (+)-**4** (pentafluoroeldanolide)

Results and Discussion

Scheme 1 depicts the results of the retrosynthetic analysis of fluoroeldanolide, (+)-**3**, from which two key points for the synthesis were suggested: the first is the synthesis of (*S*)-4,4,5-trifluoro-6-methylhepta-1,5-dien-3-ol [(+)-**7**] in optically pure form and the second is the construction of the γ-lactone moiety. We planned to synthesize trifluorinated allylic alcohol **7** by [2,3]-Wittig rearrangement of 1,1,2-trifluoroallylic ether **6** and optical resolution using subsequent lipase-catalyzed enantioselective reaction.[16–18] For the second key reaction to construct the γ-lactone moiety, we employed our original methodology of intramolecular radical cyclization.[8]

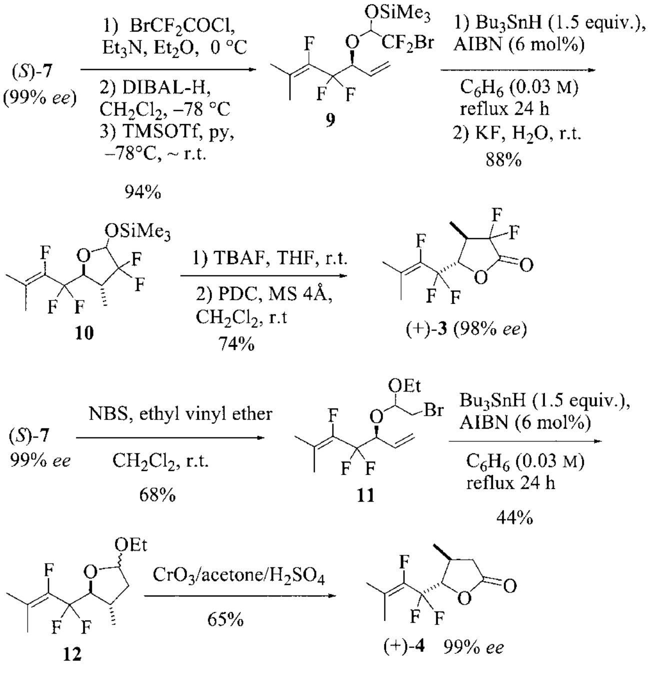
Synthesis of the racemic alcohol **7** was accomplished by [2,3]-Wittig rearrangement of the 1,1,2-trifluoroallylic ether **6**; allylic ether **6** was treated with lithium tetramethylpiperidine (LTMP) in tetrahydrofuran (THF) at −78 °C and the mixture was then warmed to 0 °C with stirring for over 14 h. Racemic 4,4,5-trifluoro-6-methylhepta-1,5-dien-3-ol [(±)-**7**] was obtained in 62% yield.[16,18] Alcohol (±)-**7** was next converted into the corresponding acetate (±)-**8**, which was subjected to lipase-catalyzed hydrolysis.[16,18] The enantiomeric excess of the alcohol produced, (*R*)-**7**, was determined by capillary GC analysis using a chiral-phase column (Chiraldex G-Ta) as its acetate **8** and its absolute configuration was determined by the modified Mosher method pro-



Scheme 2. Preparation of optically active 4,4,5-trifluoro-6-methylhepta-1,4-dien-3-ol

posed by Kusumi and Ohtani.[19] Thus, both enantiomers of the alcohol, (*S*)-**7** and (*R*)-**7**, were prepared successfully (Scheme 2).

The synthesis of 2,2,5,5,6-pentafluoroeldanolide [(+)-**3**] was accomplished using our original radical cyclization protocol (Scheme 3).[5,6,8] Alcohol (*S*)-**7** was converted into its α-bromo-α,α-difluoroacetate, which was then reduced to the corresponding acetal by diisobutylaluminum hydride (DIBAL) in dichloromethane (CH_2Cl_2) at −78 °C; subsequent treatment with trimethylsilyl triflate (TMSOTf) in the presence of pyridine gave the *O*-TMS-acetal **9** in 94% yield. A benzene solution of tributyltinhydride (1.5 equiv.) was then slowly added over 5 h to a benzene solution of the acetal **9** and azobisisobutyrylnitrile (AIBN; 10 mol %) under reflux . The reaction mixture was heated under reflux for an additional 24 h, then cooled to room temperature. After evaporation, flash column chromatography on silica gel using hexane/ethyl acetate (200:1 to 50:1) as eluent gave the cyclized product **10** (88%). This step occurred regiospecifically to provide only the five-membered lactol; no six-membered lactol was obtained. The TMS lactol was then treated with a 1.0 M THF solution of tetrabutylammonium fluoride (TBAF) at room temperature for 12 h to provide the deprotected lactol, which was then subjected to PDC oxidation. Although oxidation of this lactol proceeded very slowly — the reaction of lactol **7** with PDC in CH_2Cl_2 in the presence of powdered molecular sieves 4 Å at room temperature took 24 h — the subsequent purification using a flash column of silica gel gave the desired γ-lactone (+)-**3** in 74% yield. The optical purity of the final product (+)-**3** was confirmed by GC analysis to be 98% *ee*. Using the same protocol, the antipode of pentafluoroeldanolide (−)-**3** was synthesized from (*R*)-**7** having an *ee* of 91%.



Scheme 3. Synthesis of (+)-**3** and (+)-**4** by a radical-cyclization strategy

5,5,6-Trifluoroeldanolide [(+)-**4**] was synthesized through another type of radical cyclization protocol: the Ueno−Stork procedure[20] (Scheme 3). Alcohol (*S*)-**7** was converted into the corresponding butyl acetal (*S*)-**11** in 62% yield. The acetal (*S*)-**11** was subjected to radical cyclization in the presence of tributylstannyl hydride to give the cyclic acetal in 44% yield, which, following Jones oxidation, provided (+)-**4** in 48% yield (99% *ee*). Using the same protocol, the antipode of (−)-**4** was also synthesized.

The EAG test of these analogues showed that both enantiomers of trifluoroeldanolide **3** and pentafluoroeldanolide **4** were significantly less active relative to the natural pheromone (Figure 2). Thus, we established that the olfactory activity of *Eldana saccharina* by point-fluorinated pheromone analogues is determined critically by the fluorine-substituted part of the molecule.

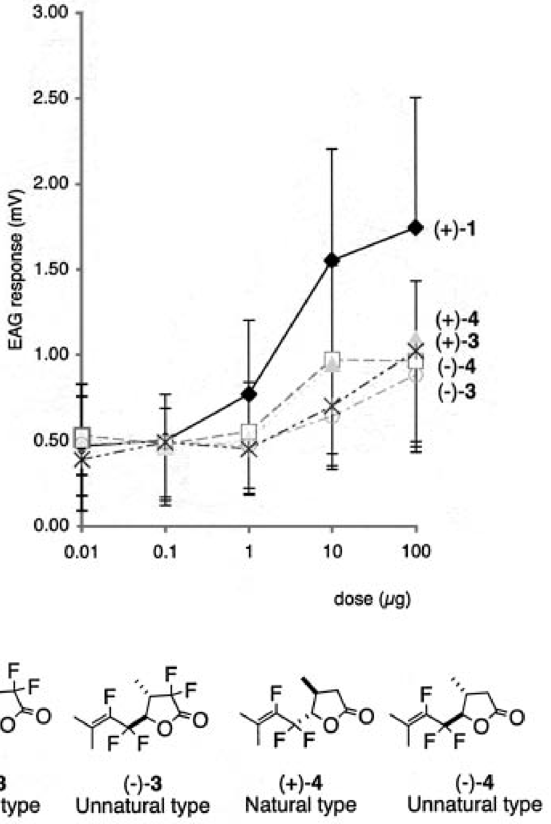


Figure 2. Results of the EAG test using optically active fluorinated eldanolide

As mentioned earlier, difluoroeldanolide **2** exhibited the same biological activity as the natural pheromone, while the pentafluoro-analogue **3** and the trifluoro-analogue **4** were inactive; these results seem to suggest that the electrostatic properties of the 3-methyl-2-butenyl group, which is connected at the 4-position of the γ-lactone ring, may be important for molecular recognition by the receptor protein, while those of the γ-position of the lactone ring are independent. It is unclear, however, whether or not these fluorinated analogues bind with the protein in the same fashion as does the natural eldanolide. If fluorinated analogues bind with the receptor protein in a manner different from that of the natural pheromone, or bind with the protein at a completely different position as a result of the substitution by the fluorine atoms, the EAG activity will be independent of the molecular recognition mechanism on the receptor protein. In addition, the conformation of an organic molecule may be altered when it attaches to the receptor protein. Thus, many unsolved questions must still be acknowledged in any discussion that uses the results of EAG tests and calculations of the electron spin density of the molecular surface.

Conclusion

We have synthesized several types of point-fluorinated analogues of eldanolide in optically active forms and evaluated their pheromone activities by EAG tests. This test revealed that the point of fluorination on the pheromone molecule influences the olfactory response critically. An investigation by computational chemistry of the fluorinated pheromone analogues and the natural pheromone suggested that EAG activity is not responsible for the electrostatic pattern on the molecular surface and that the molecular orbital of these compounds may be important for recognition of the pheromone molecule at the olfactory receptor site. Further investigations in the field of point-fluorinated pheromone analogues will provide not only a better knowledge of pheromone chemistry, but also useful insights for the development of new bioactive molecules.

Experimental Section

General Remarks: Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were carried out under argon using dry, freshly distilled solvents and magnetic stirring. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Benzene was distilled and stored over sodium. All reactions were monitored by thin-layer chromatography using silica gel plates. Flash chromatography was performed with the indicated solvents and silica gel (Wako gel C-300E). ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded with Varian VXR-200 (200 MHz) and JNM-270 (270 MHz) spectrometers; chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as the internal reference in $CDCl_3$ or hexafluorobenzene (C_6F_6). IR spectra were obtained with a JASCO FTIR-230 spectrometer. Optical rotation was measured using a JASCO DIP-370 digital polarimeter. The stereoselectivity was determined by capillary gas chromatography (MS, φ 0.25 mm × 25 m, 100−250 °C, N_2). The optically purity was determined by capillary gas chromatography (Chiraldex G-Ta, φ 0.25 mm × 20 m, 100−150 °C, He).

3,4,4-Trifluoro-2-methylbut-3-en-2-ol (5): A solution of 1,1,1,2,2-pentafluoroethane in THF (11.98 mmol, 5.21 mL) was diluted with THF (25.0 mL) and cooled to −100 °C. A solution of butyllithium in hexane (13.1 mL, 21.0 mmol) was added dropwise over 10 min and then the mixture was warmed slowly to −78 °C with stirring. After 2 h, to the solution of generated vinyllithium was added a solution of acetone (0.58 g, 10.0 mmol) in THF (25.0 mL) and then the mixture was warmed slowly to −50 °C with stirring for 6 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ethyl acetate, washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated. Flash column chromatography (hexane/ethyl acetate, 30:1−5:1) afforded allyl alcohol **5** (1.07 g, 7.19 mol) as a pale-yellow oil in 92% yield; $R_f = 0.37$ (hexane/ethyl acetate, 7:1); b.p. 65 °C/135 Torr (kugelrohr distillation). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.47$ (dd, $J = 4.6$ Hz, 1.8 Hz, 6 H), 2.16 (br. d, $J = 6.2$ Hz, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.86$ (t, $J = 2.0$ Hz), 67.88, 133.52 (ddd, $J = 235.9$, 43.4, 14.0 Hz), 153.39 (ddd, $J = 288.1$, 279.7, 48.6 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): $\delta = -18.04$ (dd, $J = 109.7$, 33.6 Hz, 1 F), 46.96 (dd, $J = 110.1$, 84.1 Hz, 1 F), 59.41 (dd, $J = 84.3$, 33.7 Hz, 1 F) ppm. IR (neat): $\tilde{\nu} = 3401$, 2979, 2873, 1777, 1306, 1269, 1165, 1061 cm^{-1}. $C_5H_7F_3O$ (140.1): calcd. C 42.86, H 5.04; found C 43.18, H 5.19.

3-Allyloxy-1,1,2-trifluoro-3-methylbut-1-ene (6): A solution of alcohol **5** (1.40 g, 9.99 mmol) in THF (11.0 mL) was added dropwise to sodium hydride (480 mg, 12.0 mmol of a 60% dispersion from which the oil had been removed using toluene) in THF (11.0 mL) at 0 °C. The reaction mixture was stirred at 23 °C for 2 h and then a DMF (11.0 mL) solution of allyl bromide (2.47 g, 19.98 mmol) was added dropwise. The reaction mixture was stirred at 70 °C for 12 h (overnight). The solution was poured into cold water and the aqueous layer was extracted with diethyl ether. The organic layer was washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (silica gel; hexane/ethyl acetate, 20:1−5:1) afforded trifluoroallylic ether **6** (1.30 g, 7.19 mmol) as a pale-yellow oil in 72% yield; $R_f = 0.77$ (hexane/ethyl acetate, 7:1); b.p. 70 °C/18 Torr (kugelrohr distillation). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.43-1.49$ (m, 6 H), 3.88 (d, $J = 5.6$ Hz, 2 H), 5.15 (ddd, $J = 10.4$, 3.2, 1.7 Hz, 1 H), 5.28 (ddd, $J = 17.1$, 3.4, 1.7 Hz, 1 H), 5.90 (ddt, $J = 17.1$, 10.3, 5.6 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 24.30$ (t, $J = 1.9$ Hz), 31.59, 64.71, 116.6, 132.5 (ddd, $J = 239.4$, 44.1, 13.7 Hz), 134.71, 154.41 (ddd, $J = 289.9$, 280.7, 48.5 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): $\delta = -17.16$ (ddd, $J = 216.7$, 111.6, 33.6 Hz, 1 F), 47.14 (ddd, $J = 183.1$, 112.2, 85.5 Hz, 1 F), 60.47 (ddd, $J = 571.7$, 85.1, 33.5 Hz, 1 F) ppm. IR (neat): $\tilde{\nu} = 2993$, 1772, 1311, 1277, 1161, 1060 cm^{-1}. $C_8H_{11}F_3O$ (180.17): calcd. C 53.33, H 6.15; found C 53.21, H 6.32.

4,4,5-Trifluoro-6-methylhepta-1,5-dien-3-ol (7): A solution of *n*-butyllithium in hexane (12.5 mL, 20.0 mmol) was added dropwise to a solution of tetramethylpiperidine (2.97 g, 21.0 mmol) in THF (50.0 mL) at −20 °C. The solution was warmed to 0 °C for 30 min to ensure complete formation of lithium tetramethylpiperidine (LTMP) and was subsequently re-cooled to −100 °C. A solution of the appropriate allylic ether **6** (2.42 g, 10.0 mmol) in tetrahydrofuran (50.0 mL) was added dropwise over 50 min. After the solution was stirred at −100 °C for 6 h, the solution was warmed slowly to room temperature over 18 h. The reaction was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate, extracted with the same solvent, dried with anhydrous $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2; hexane/ethyl acetate, 30:1 to 5:1) afforded allylic alcohol **7** (1.14 g, 6.32 mmol) as a pale-yellow oil in 63% yield; $R_f = 0.26$ (hexane/ethyl acetate, 7:1); b.p. 85 °C/15 Torr (kugelrohr distillation). ^{1}H NMR (200 MHz,

$CDCl_3$): δ = 1.74−1.82 (m, 6 H), 2.05−2.28 (br. s, 1 H, OH), 4.41−4.58 (m, 1 H), 5.40 (d, *J* = 10.4 Hz, 1 H), 5.51(dt, *J* = 17.2, 1.6 Hz, 1 H), 5.86−6.03 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.39 (q, *J* = 4.4 Hz), 17.54 (d, *J* = 9.7 Hz), 73.15 (dd, *J* = 28.5, 28.6 Hz), 118.25 (dt, *J* = 247.4, 39.8 Hz), 119.58 (d, *J* = 12.2 Hz), 119.78, 131.80 (t, *J* = 3.1 Hz), 145.46 (dt, *J* = 239.6, 31.2 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 34.08 (s, 1 F), 52.22 (dd, *J* = 506.8, 266.2 Hz, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3410, 2930, 2195, 1642, 1385, 1135, 1065 cm^{-1}. $C_8H_{11}F_3O$ (180.17): calcd. C 53.33, H 6.15; found C 53.25, H 5.93.

2,2,3-Trifluoro-4-methyl-1-vinylpent-3-enyl Acetate (8): A solution of acetyl chloride (1.18 g, 15.0 mmol) in dichloromethane (13.0 mL) was added dropwise to a solution of allylic alcohol (±)-**7** (1.80 g, 10.0 mmol) and pyridine (2.43 mL, 15.0 mmol) in dichloromethane (20.0 mL) at 0 °C. The solution was warmed to room temperature over 6 h. The reaction was quenched with crushed ice, diluted with ethyl acetate, extracted with the same solvent, dried with anhydrous $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2; hexane/ethyl acetate, 60:1−5:1) afforded acetate **8** (2.12 g, 9.52 mmol) as a pale-yellow oil in 95% yield; R_f = 0.72 (hexane/ethyl acetate, 7:1); b.p. 125 °C/8 Torr (kugelrohr distillation). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72−1.81 (m, 6 H), 2.12 (s, 3 H), 5.43 (d, *J* = 10.3 Hz, 1 H), 5.47 (d, *J* = 17.1 Hz, 1 H), 5.68−5.85 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.24 (q, *J* = 4.3 Hz), 17.39 (d, *J* = 9.3 Hz), 20.63, 73.39 (dd, *J* = 30.8, 28.1 Hz), 116.89 (dt, *J* = 248.2, 39.5 Hz), 119.72 (d, *J* = 13.9 Hz), 121.93, 128.25 (t, *J* = 2.7 Hz), 144.90 (dt, *J* = 241.2 Hz, 30.5 Hz), 169.00 ppm. IR (neat): $\tilde{\nu}$ = 2936, 1758, 1376, 1225, 1050 cm^{-1}. $C_{10}H_{13}F_3O_2$ (222.20): calcd. C 54.05, H 5.90; found C 53.85, H 5.77.

Optical Resolution of Allylic Alcohol (±)-7 by a Lipase-Catalyzed Reaction: A mixture of acetate (±)-**8** (3.18 g, 14.3 mmol) and lipase PS (1.59 g, Amano Enzyme Ltd.) in 0.1 m phosphate buffer (pH 7.2, 30 mL) was stirredat 35 °C for 4.5 h and then the mixture was filtered through a celite pad in a sintered glass filter and washed with diethyl ether. The filtrate was extracted with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and then the solvents were evaporated. Flash column chromatography (SiO_2; hexane/ethyl acetate, 50:1−10:1) gave alcohol (*R*)-**7** (775 mg, 4.30 mmol) in 30% yield and unchanged acetate (*S*)-**8** (2.00 g, 9.03 mmol) in 63% yield. The enantiomeric excesses of (*R*)-**7** (98% *ee*) and (*S*)-**8** (68% *ee*) were determined by capillary GC analysis using a chiral phase (Chiraldex G-Ta). Because the optical purity of (*S*)-**8** was too poor for further use, the sample was again subjected to lipase-catalyzed hydrolysisat 35 °C for 9.5 h . Optically pure (> 99% *ee*) (*S*)-**8** (1.20 g, 5.42 mmol) was obtained in 38% overall yield (two steps). To a solution of acetate (*S*)-**8** (2.67 g, 12.0 mmol) in THF (24.0 mL) were added a solution of lithium hydroxide monohydrate (1.01 g, 24.0 mmol) in water (8.0 mL) and methanol (2.0 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h. After quenching the reaction with 2 n HCl, the aqueous phase was extracted with diethyl ether and the organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2; hexane/ethyl acetate, 20:1−10:1) afforded alcohol (*S*)-**7** (1.99 g, 11.1 mmol) as a colorless oil in 92% yield. Initially we hoped to obtain optically active alcohol (±)-**7** by lipase-catalyzed acylation, but because of the poor nucleophilicity of **7**, resulting from the effect of the neighboring difluoromethylene group, it required long reaction time (> 2 days), we employed lipase-catalyzed hydrolysis reaction of (±)-**8** for this step istead. (*S*)-**7** (> 99% ee): $[\alpha]_D^{24}$ = −13.0 (*c* = 1.12, $CHCl_3$); (*R*)-**7** (98% *ee*): $[\alpha]_D^{24}$ = +13.2 (*c* = 1.00, $CHCl_3$).

(3*S*)-[2-Bromo-2,2-difluoro-1-(2,2,3-trifluoro-4-methyl-1-vinylpent-3-enyloxy)ethoxy]trimethylsilane (9): A suspension of lithium bromodifluoroacetate (3.62 g, 20.0 mmol) in diethyl ether (20.0 mL) was cooled to 0 °C and then a solution of oxalyl chloride (2.54 g, 20.0 mmol) in diethyl ether (3.0 mL) was added dropwise slowly. The mixture was stirred for 2 h at 23 °C. To the mixture were added a solution of alcohol (*S*)-**7** (1.80 g, 10.0 mmol) and triethylamine (4.18 mL, 30.0 mmol) in diethyl ether (10.0 mL), and the mixture was stirred for 2 h at 23 °C. The reaction mixture was filtered through short column of silica gel (eluted with ether) and concentrated to give 2,2,3-trifluoro-4-methyl-1-vinylpent-3-enyl bromodifluoroacetate (3.38 g) as a colorless oil, which was used for the next reaction without further purification. To a solution of bromodifluoroacetate (3.37 g, 10.0 mmol) in CH_2Cl_2 (25.0 mL) was added DIBAL-H in toluene (7.35 mL, 11.0 mmol) at −78 °C over 10 min and the mixture was stirred at −78 °C for 1.5 h. To the mixture were added pyridine (2.45 mL, 30.0 mmol) and a solution of TMSOTf (3.33 g, 15.0 mmol) in CH_2Cl_2 (8.0 mL), and then it was slowly warmed up to room temp. with stirring for 7 h. The reaction was quenched by the addition of powdered KF (2.10 g) and water (1.0 mL), and then the mixture was stirred for an additional 15 min open to the atmosphere. The mixture was filtered through a short column of Florisil (eluted with CH_2Cl_2) and was then concentrated. Flash column chromatography (SiO_2; hexane/ethyl acetate, 100:1−30:1) gave silyl acetal **9** (3.50 g, 8.51 mmol) in 85% yield (two steps); R_f = 0.72 (hexane/ethyl acetate, 7:1); b.p. 135 °C/2 Torr (kugelrohr distillation). ^1H NMR (200 MHz, $CDCl_3$, diastereoisomeric mixture): δ = 0.21 (s, 9 H), 1.70−1.82 (m, 6 H), 4.35−4.46 (m, 1 H), 4.76−4.86 (m, 1 H), 5.45−5.62 (m, 2 H), 5.75−6.00 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, diastereoisomeric mixture): δ = 0.09, 16.27−16.45 (m), 17.54 (d, *J* = 9.4 Hz), 77.27 (dt, *J* = 77.9, 33.8 Hz), 94.44 (dt, *J* = 114.5, 31.2 Hz), 116.70 (ddt, *J* = 247.6, 39.5, 14.5 Hz), 119.05 (t, *J* = 14.2 Hz), 121.71 (dd, *J* = 309.6, 15.5 Hz), 122.76 (d, *J* = 71.9 Hz), 129.49 (d, *J* = 26.5 Hz), 143.77 (dt, *J* = 239.2, 31.9 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6, diastereoisomeric mixture): δ = 33.31 (d, *J* = 112.9 Hz, 1 F), 49.02−50.71 (m, 1 F), 56.56 (d, *J* = 268.6 Hz, 1 F), 98.20−100.76 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2959, 1375, 1260, 1203, 1139 cm^{-1}. $C_{13}H_{20}BrF_5O_2Si$ (411.28): calcd. C 37.96, H 4.90; found C 38.52, H 4.84.

(4*R*,5*S*)-[3,3-Difluoro-4-methyl-5-(1,1,2-trifluoro-3-methylbut-2-enyl)tetrahydrofuran-2-yloxy]trimethylsilane (10): A benzene (110.0 mL) solution of tributyltin hydride (3.00 mL, 10.50 mmol) was added dropwise over 8 h with stirring to a refluxing solution of silyl acetal **9** (2.87 g, 7.00 mmol) and AIBN (58.0 mg, 0.35 mmol) in benzene (30.0 mL), and then the mixture was stirred for additional 2 h under reflux. After being cooled to room temp., to the mixture was added saturated aqueous KF (140 mL) and then the mixture was stirred for 10 min before being extracted with diethyl ether. The combined organic layers were dried with anhydrous $MgSO_4$ and flash column chromatography (SiO_2; hexane/ethyl acetate, 1:0−30:1) gave (4*S*,5*S*)-**10** (2.05 g, 6.16 mmol) in 88% yield; R_f = 0.72 (hexane/ethyl acetate, 7:1); b.p. 75 °C/2.5 Torr (kugelrohr distillation). ^1H NMR (200 MHz, $CDCl_3$, diastereoisomeric mixture): δ = 1.75−1.83 (m, 9 H), 1.18−1.25 (m, 3 H), 1.75−1.83 (m, 6 H), 2.66−2.94 (m, 1 H), 3.99−4.34 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, diastereoisomeric mixture): δ = −0.03, 0.10, 7.57 (d, *J* = 6.4 Hz), 11.81 (d, *J* = 7.7 Hz), 17.94, 25.74, 32.66, 33.88, 39.83 (t, *J* = 21.1 Hz), 43.14 (t, *J* = 22.6 Hz), 82.68 (d, *J* = 8.0 Hz), 83.79 (t, *J* = 3.8 Hz), 95.53 (dd, *J* = 40.3, 26.7 Hz), 97.12 (dd, *J* = 43.5, 24.2 Hz), 118.61, 119.11, 125.75 (dd, *J* = 261.4, 248.3 Hz), 126.28 (dd, *J* = 266.1, 247.0 Hz), 134.25, 134.63 ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6, diastereoisomeric mixture): δ = 37.04

(ddd, J = 229.6, 23.0, 6.8 Hz, 0.5 F), 38.71 (d, J = 229.2 Hz, 0.5 F), 38.85 (dd, J = 229.2, 9.8 Hz, 0.5 F), 61.15 (ddd, J = 232.4, 24.4, 6.1 Hz, 0.5 F) ppm. IR (neat): $\tilde{\nu}$ = 2956, 1259, 1206, 1129, 1042 cm^{-1}. $C_{13}H_{21}{}_{F_5}O_2Si$ (332.38): calcd. C 46.98, H 6.37; found C 46.45, H 6.84.

(4*R*,5*S*)-3,3-Difluoro-4-methyl-5-(1,1,2-trifluoro-3-methylbut-2-enyl)dihydrofuran-2-one (3): Tetrabutylammonium fluoride in THF (5.20 mL, 5.20 mmol) was added to a THF (22.0 mL) solution of silyl lactol (4*S*,5*S*)-**10** (1.33 g, 4.00 mmol) and then the mixture was stirred at room temperature for 24 h. The mixture was diluted with diethyl ether and then the organic layer was washed with water and brine, and dried with anhydrous $MgSO_4$. Evaporation of the solvent gave the corresponding lactol (1.05 g), which was used for the next reaction without purification. Powdered MS 4Å (2.90 g) and PDC (5.36 g, 14.00 mmol) were added to a dichloromethane (25.0 mL) solution of lactol (1.05 g) and then the mixture was stirred for 42 h at room temp. The mixture was filtered through a short column of silica gel (eluted with ether) and concentrated to dryness. Flash column chromatography (SiO_2; hexane/ethyl acetate, 40:1) gave lactone (+)-(4*R*,5*S*)-**3** (455 mg, 1.76 mmol) as a colorless oil in 44% yield (2 steps). The optical purity of this compound (98% *ee*) was determined by capillary GC analysis using a chiral column (Chiraldex G-Ta); R_f = 0.46 (hexane/ethyl acetate, 7:1); b.p. 75 °C/2.2 Torr (kugelrohr distillation). $[\alpha]_D^{22}$ = +39.1 (c = 1.01, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (d, J = 7.3 Hz, 3 H), 1.77−1.85 (m, 6 H), 2.78−3.08 (m, 1 H), 4.46−4.59 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.25 (d, J = 7.5 Hz), 20.95, 22.17 (d, J = 9.2 Hz), 36.80 (t, J = 21.1 Hz), 65.85, 77.20 (t, J = 10.7 Hz), 79.05 (ddd, J = 37.1, 28.6, 7.7 Hz), 114.81 (dt, J = 251.3, 22.4 Hz), 115.74 (dd, J = 260.3, 250.4 Hz), 123.45, 144.10 (dt, J = 240.1, 30.2 Hz), 160.20 (t, J = 33.5 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 30.35 (d, J = 12.6 Hz, 1 F), 44.60 (dd, J = 278.1, 18.3 Hz, 1 F), 46.95 (dd, J = 277.7, 13.9 Hz, 1 F), 48.77 (dd, J = 277.7, 13.9 Hz, 1 F), 55.36 (dd, J = 276.7, 12.2 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2930, 1831, 1458, 1202, 1138, 1033 cm^{-1}. $C_{10}H_{11}F_5O_2$ (258.19): calcd. C 46.52, H 4.29; found C 45.10, H 4.44.

Using (*R*)-**7** (92% *ee*) as the starting material gave the unnatural-type eldanolide analogue, (−)-(4*S*,5*R*)-**3** (91% *ee*) in 45% overall yield. $[\alpha]_D^{22}$ = −34.3 (c = 1.38, $CHCl_3$).

(3*S*)-3-(2-Bromo-1-ethoxyethoxy)-4,4,5-trifluoro-6-methylhepta-1,5-diene (11): To a solution of *N*-bromosuccinimide (2.14 g, 12.0 mmol) and (*S*)-**7** (1.80 g, 10.0 mmol) in dichloromethane (23.0 mL) was added dropwise a solution of ethyl vinyl ether (1.44 g, 20.0 mmol) in dichloromethane (10.0 mL) at −20 °C and then the mixture was stirred for 10 h at −78 °C. The solution was slowly warmed up to room temp. with stirring for 2 h and then the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with diethyl ether and then the combined organic layers were dried with anhydrous $MgSO_4$ and the solvents were evaporated to dryness. Flash column chromatography (SiO_2; hexane/ethyl acetate, 50:1) gave acetal **11** (2.60 g, 7.88 mmol) as a colorless oil in 79% yield; R_f = 0.70 (hexane/ethyl acetate, 10:1); b.p. 65 °C/3.0 Torr. $[\alpha]_D^{22}$ = +9.6 (c = 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.62 (s, 3 H), 1.70 (s, 3 H), 2.34−2.56 (m, 2 H), 5.02−5.12 (m, 1 H), 5.25−5.40 (m, 3 H), 5.84 (ddd, J = 17.5, 10.4, 6.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.91, 25.76, 32.81, 79.27, 108.89 (t, J = 314.6 Hz), 117.20, 118.71, 134.01, 136.07, 158.80 (t, J = 31.1 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 101.05 (s, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2927, 1775, 1451, 1297, 1169, 1131 cm^{-1}. $C_{12}H_{18}BrF_3O_2$ (331.17): calcd. C 43.52, H 5.48; found C 43.10, H 5.65.

(4*R*,5*S*)-5-Ethoxy-3-methyl-2-(1,1,2-trifluoro-3-methylbut-2-enyl)-tetrahydrofuran (12): A solution of tributyltin hydride (3.45 mL, 12.0 mmol) in benzene (130 mL) was added dropwise over 9 h with stirring to a solution of acetal **11** (2.65 g, 8.00 mmol) and AIBN (67.0 mg, 0.40 mmol) in benzene under reflux (30.0 mL), and then the mixture was stirred for an additional 2 h. The mixture was cooled to room temp. and then saturated aqueous KF (150 mL) was added and the flask was left open to the atmosphere. After being stirred for 10 min, the mixture was extracted with diethyl ether and dried with anhydrous $MgSO_4$, and then the solvents were evaporated to dryness. Flash column chromatography (SiO_2; hexane/ethyl acetate, 1:0−30:1) afforded lactol (4*S*, 5*S*)-**12** (1.37 g, 5.43 mmol) in 68% yield as a colorless oil; R_f = 0.68 (hexane/ethyl acetate, 10:1); b.p. 75 °C/2.5 Torr (kugelrohr distillation). ^{1}H NMR (200 MHz, $CDCl_3$, diastereoisomeric mixture): δ = 0.10 (s, 4.5 H), 0.11 (s, 4.5 H), 0.98 (d, J = 6.9 Hz, 1.5 H), 1.00 (dd, J = 7.2 Hz, 2.2 Hz, 1.5 H), 1.55 (s, 3 H), 1.64 (s, 3 H), 1.84−2.19 (m, 1 H), 2.24 (t, J = 6.2 Hz, 2 H), 3.59 (dt, J = 9.3, 6.0 Hz, 0.5 H), 3.85 (dt, J = 6.3, 6.4 Hz, 0.5 H), 4.97 (d, J = 6.7 Hz, 0.5 H), 5.03−5.14 (m, 1 H), 5.13 (d, J = 6.0 Hz, 0.5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, diastereoisomeric mixture): δ = −0.03, 0.10, 7.57 (d, J = 6.4 Hz), 11.81 (d, J = 7.7 Hz), 17.94, 25.74, 32.66, 33.88, 39.83 (t, J = 21.1 Hz), 43.14 (t, J = 22.6 Hz), 82.68 (d, J = 8.0 Hz), 83.79 (t, J = 3.8 Hz), 95.53 (dd, J = 40.3, 26.7 Hz), 97.12 (dd, J = 43.5, 24.2 Hz), 118.61, 119.11, 125.75 (dd, J = 261.4, 248.3 Hz), 126.28 (dd, J = 266.1, 247.0 Hz), 134.25, 134.63 ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6, diastereoisomeric mixture): δ = 37.04 (ddd, J = 229.6, 23.0, 6.8 Hz, 0.5 F), 38.71 (d, J = 229.2 Hz, 0.5 F), 38.85 (dd, J = 229.2, 9.8 Hz, 0.5 F), 61.15 (ddd, J = 232.4, 24.4, 6.1 Hz, 0.5 F) ppm. IR (neat): $\tilde{\nu}$ = 2962, 1461, 1370, 1253, 1109 cm^{-1}. $C_{12}H_{19}F_3O_2$ (252.27): calcd. C 57.13, H 7.59; found C 57.93, H 7.41.

(4*S*,5*S*)-4-Methyl-5-(1,1,2-trifluoro-3-methylbut-2-enyl)-dihydrofuran-2-one (4): Jones reagent (8 N, 5.2 mL) was added to an acetone (3.0 mL) solution of (4*S*, 5*S*)-**12** (757 mg, 3.00 mmol) and then the mixture was stirred at room temp. for 24 h open to the atmosphere. The mixture was quenched by the addition of aqueous $NaHSO_4$ and $NaCO_3$ solutions. The mixture was diluted with diethyl ether and the organic layers were dried with anhydrous $MgSO_4$ and then the solvents were evaporated to dryness. Flash column chromatography (SiO_2; hexane/ethyl acetate, 50:1−20:1) gave (4*S*,5*S*)-(+)-**4** (393 mg, 1.77 mmol, 99% *ee*) in 59% yield: R_f = 0.68 (hexane/ethyl acetate, 7:1); b.p. 75 °C/2.2 Torr (kugelrohr distillation). $[\alpha]_D^{22}$ = +26.7 (c = 1.18, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, J = 6.8 Hz, 3 H), 1.27−1.80 (m, 6 H), 2.01−2.24 (m, 1 H), 2.72−2.87 (m, 2 H), 4.30−4.44 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.00−16.19 (m), 17.42 (d, J = 9.3 Hz), 19.89, 29.01, 35.46, 83.49 (dd, J = 34.9, 27.4 Hz), 116.50 (dt, J = 244.3, 41.2 Hz), 120.16 (dd, J = 13.7, 2.9 Hz), 143.47 (dt, J = 238.6, 29.4 Hz), 175.26 ppm. ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 33.06 (s, 1 F), 48.79 (dd, J = 274.7, 14.3 Hz, 1 F), 54.49 (d, J = 274.7 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2973, 1796, 1455, 1385, 1206 cm^{-1}. $C_{10}H_{13}F_3O_2$ (222.20): calcd. C 54.05, H 5.90; found C 53.85, H 5.72. Using (*R*)-**7** (98% *ee*) as the starting material, the unnatural-type eldanolide analogue, (4*R*,5*R*)-(−)-**4**, was synthesized in 27% overall yield by following the procedure described above: $[\alpha]_D^{22}$ = −25.8 (c = 1.00, $CHCl_3$), 97% *ee*.

EAG Tests of the Pheromone Analogues: Electroantennograms were recorded from male moths restrained in a styrofoam block. The apex of one antenna was cut off and its tip was inserted into the recording electrode. The neck of the insect was impaled with the reference electrode. Glass microelectrodes were filled with the insect's Ringer. Both electrodes were connected to a Neurolog NL 102 preamplifier through chloridized silver wires. The signal was filtered (DC to 1 kHz) and fed into an oscilloscope. Compounds were diluted in hexane at the appropriate concentrations. A volume of each solution was deposited on a filter paper inserted into a Pasteur pipette. A purge stream of humidified pure air (1.0 L/min; 100% RH) was blown continuously on the antenna. Stimulations were achieved by blowing a puff of air (0.5 sec, 0.5 L/min) through the pipette into the purge air stream. the stimuli were presented in the order of increasing doses. The EAG responses were recorded on twelve different insects.

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