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Asymmetric Synthesis of Both Enantiomers of α,α-Difluoroeldanolide: An Interesting Property of Their Biological Activity

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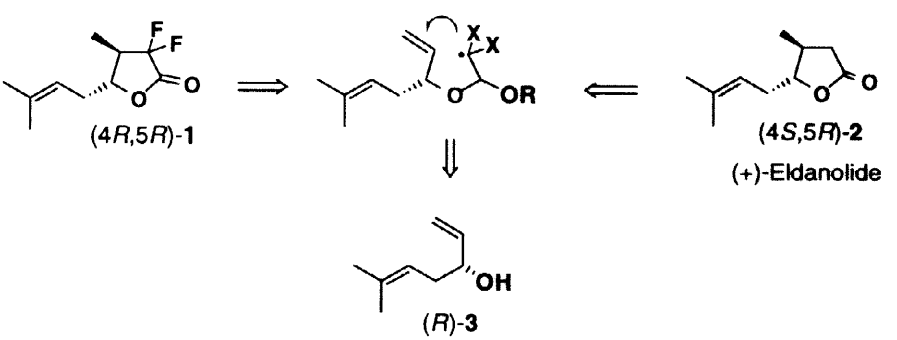
Abstract: The synthesis of difluorinated analogue of an insect sex pheromone has been accomplished through intramolecular radical cyclization and lipase-catalyzed reaction. Optically active α,α-difluoroeldanolide and its antipode have been synthesized. Dose-response curves constructed from electroantennogram responses of female moths showed the difluoroanalogues to be as active as the natural pheromone.

Partially fluorinated analogues of biologically important compounds demonstrated dramatic changes and distinctive modifications in their biological activities; it is believed that difluoromethylene moiety was recognized as similar to ether-oxygen *in vivo*, so that an interesting biological activity should thus be expected for analogues of α,α-difluorinated-γ-lactones.[1] Recently we demonstrated the systematic synthesis of α,α-difluoro-γ-lactones using intramolecular cyclization of α,α-difluoroacetal radicals onto olefin as a key reaction.[2] We herein report that the first asymmetric synthesis of α,α-difluoroeldanolide, (*4R,5R*)-**1**, and its antipode, (*4S,5S*)-**1**, has been accomplished through intramolecular radical cyclization protocol (Scheme 1). α,α-Difluoroeldanolide, (*4R, 5R*)-**1**, is believed to be α,α-difluoroanalogue of eldanolide, (*4S, 5R*)-**2**, which is known to be a sex pheromone of the male African sugarcane borer, *Eldana saccharina*.[3,4,5] Electroantennography (EAG) investigation [6] revealed that the fluorinated analogues were as active as the natural pheromone onto the insect olfactory receptors.



Scheme 1

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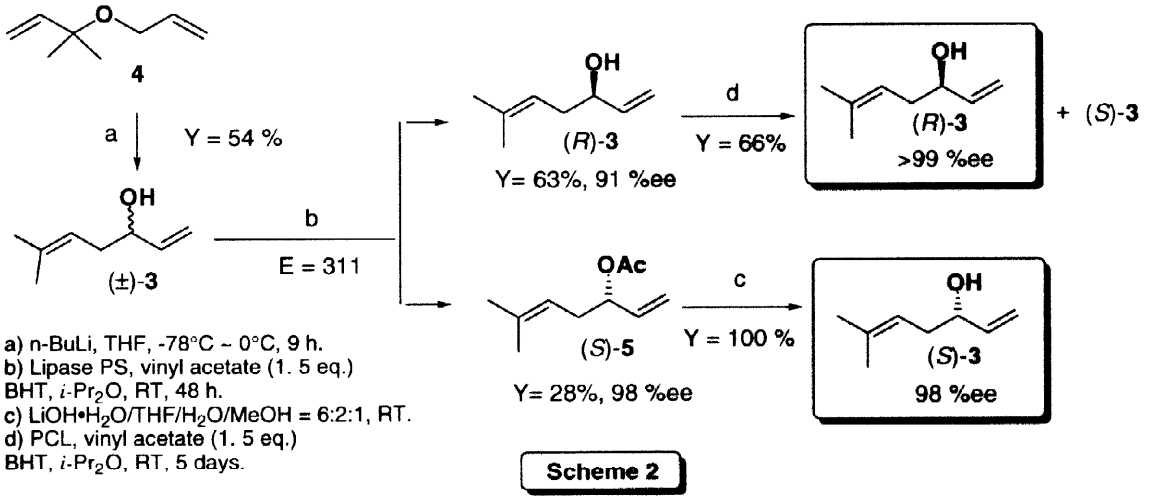
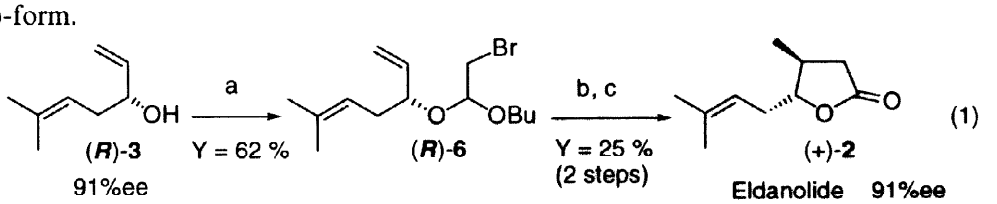
The starting material (*S*)-**3** was prepared as follows: 1,2-Wittig rearrangement of allyl ether **4** [7] gave (±)-**3** in 54% yield.[8] Enantioselective acylation of (±)-**3** was achieved using *Pseudomonas cepacia* lipase (PCL) in the presence of excess amount of vinyl acetate as acyl donor and 2,6-di-t-butyl-4-methylphenol (BHT) as anti-oxidant in diisopropyl ether as solvent. The enantioselectivity was sufficient and a high E value [9] (E = 311) was recorded in the lipase-catalyzed reaction. Enantiomeric excess of acetate **5** ($[\alpha]^{23}_D$ +18.6° (*c* 1.40, EtOH)) produced was determined by capillary GC analysis using the chiral phase column (Chiraldex G-Ta) as 98% ee. Acetate (*S*)-**5** obtained was hydrolyzed with lithium hydroxide monohydrate in a mixed solvent (THF / water / methanol = 6 : 2 : 1) to give optically active alcohol (*S*)-**3** in quantitative yield. The optical purity of (*R*)-**3** was not sufficient (91% ee) at the first stage of resolution, so that alcohol **3** was subjected to PCL-catalyzed acylation for 5 days at room temperature. Optically pure (*R*)-**3** (>99% ee) was thus obtained in 42% overall yield from racemic (±)-**3** (Scheme 2).



Scheme 2

Because optical rotation values of **3** and **5** have not been reported, absolute configuration of these compounds was confirmed by converting alcohol (*R*)-**3** to natural eldanolide, (*4S, 5R*)-**2**, through radical cyclization protocol. Alcohol (*R*)-**3**, ($[\alpha]^{23}_D$ -21.7° (*c* 0.90, EtOH), 91% ee) remaining after lipase-catalyzed acylation was converted to the corresponding butyl acetal (*R*)-**6** in 62 % yield using the Ueno-Stork procedure.[2,10] Acetal (*R*)-**6** was subjected to radical cyclization in the presence of tributylstannylhydride to give cyclic acetal and the following Jones oxidation provided natural eldanolide, (+)-**2**: $[\alpha]^{22}_D$ + 53.9° (*c* 0.70, EtOH), lit [5b] +57.8°), in 25% overall yield (Eq. 1). Absolute configuration of the starting alcohol **3** was thus confirmed as (*R*)-form.

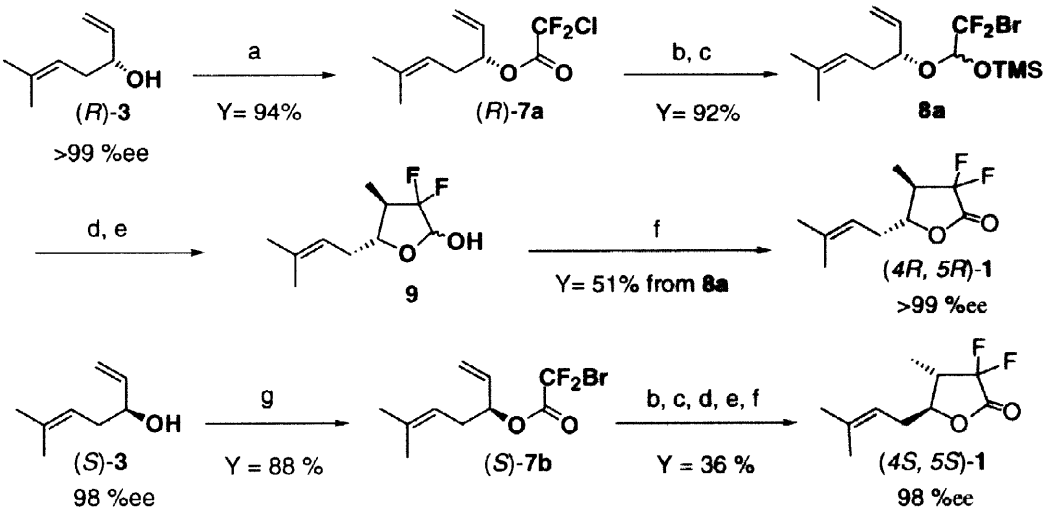


(1)

a) NBS, Butyl vinyl ether,CH_2Cl_2, Rt. b) nBu$_3$SnH, AIBN, benzene, reflux. c) Jones oxidation.

Synthesis of α,α-difluoroeldanolide, (*3R, 4R*)-**1**, was accomplished using alcohol (*R*)-**3** (>99% ee) as the starting material (Scheme 3). (*R*)-**3** was converted to α-chloro-α,α-difluoro acetate (*R*)-**7a**: $[\alpha]^{22}_D$ +9.6° (*c*

1.29, $CHCl_3$), in 94% yield.[2] Ester (*R*)-**7a** was then reduced to the corresponding acetal by DIBAL in CH_2Cl_2 at -78°C, and following treatment with trimethylsilyl-O-triflate (TMSOTf) in the presence of pyridine gave O-TMS-acetal **8a** in 92% yield. To a benzene solution of the acetal **8a** and AIBN (10 mol%) was slowly added a benzene solution of tributyltinhydride (2.2 equiv.) over 5 h under reflux conditions. The reaction mixture was heated to reflux for an additional 4 hours, then cooled to room temperature. After evaporation, silica gel flash column chromatography using hexane / ethyl acetate (200 : 1 to 50 : 1) as eluent gave the cyclized product. This step finished regiospecifically to provide only 5-membered lactol and no 6-membered lactol was obtained. TMS lactol was then treated with 1.0 M THF solution of tetrabutylammoniumfluoride (TBAF) at room temperature for 21 h to provide the deprotected lactol **9** which was used immediately for oxidation without further purification. PDC oxidation of the lactol in CH_2Cl_2 in the presence of molecular sieves 4Å powder at room temperature for 6 h, and subsequent purification using silica gel flash column gave the desired γ-lactone **1**: $[\alpha]^{23}_D$ +62.4°(*c* 1.17, EtOH), in 51% overall yield from **8a**. Optical purity of the final product (*4R,5R*)-**1** was confirmed by GC analysis as >99% ee because no signal of the enantiomer was observed using chiral column (Chiraldex G-Ta), so that the starting optical purity was exactly retained during these reaction sequences. Using this protocol, the antipode of α,α-difluoroeldanolide (*4S,5S*)-**1**: $[\alpha]^{22}_D$ -63.3° (*c* 1.15, EtOH), was also synthesized from 98% ee of (*S*)-**3**. We thus accomplished the first synthesis of optically active α,α-difluoroeldanolide through intramolecular radical cyclization protocol and PCL-catalyzed enantioselective acylation.



a) $ClCF_2CO_2Li$, $(COCl)_2$, Et_3N, Et_2O, 0 °C. b) DIBAL-H, CH_2Cl_2, -78 °C. c) TMSOTf, Py, -78 °C→rt. d) *n*-Bu_3SnH, AIBN, benzene, reflux. e) KF, H_2O, RT. f) PDC, MS4A , CH_2Cl_2, RT. g) $BrCF_2CO_2Li$, $(COCl)_2$, Et_3N, Et_2O, 0 °C.

Scheme 3

The biological activity of eldanolide, fluorinated eldanolide and their antipodes was compared by electroantennography. Increasing doses were tested on female antennae according to standard procedures [6]. As previously reported [3b], both enantiomers of eldanolide elicited strong EAG responses, the natural eldanolide analogue (4*S*,5*R*)-(+)-**1** being slightly but significantly more active at doses of 100, 1,000 and 10,000 ng (Fig. 1). The difluoroanalogues showed dose-response curves very similar to that of natural eldanolide. Substituting fluorine for hydrogen results in pheromone analogues whose intrinsic activity varies according to the number of substitutions and their position. Generally, substitutions at the polar group of lepidoptera pheromone molecules

result in reduced recognition by the olfactory receptors [11] and may produce potent inhibitors of the pheromone catabolizing enzymes [12] present in the olfactory tissues. This decreased affinity for the receptor contrasts with our results and it makes the fluoroeldanolides good candidates to investigate the interaction between eldanolide and its receptor sites.

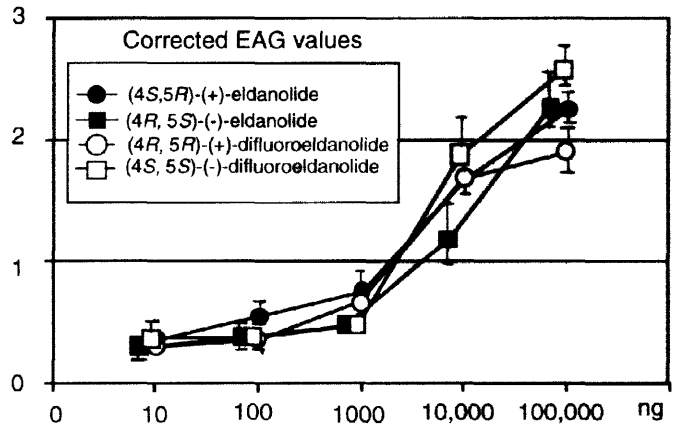


Figure 1. Results of EAG test

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