# Fluorine Labeling in Biosynthetic Studies(I): Synthesis of Fluorfarnesols

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**Abstract** ☐ The Synthesis of E,E,E-12-fluorofarnesol and E,Z-6-fluorofarnesol which are key intermediates for the study of biosynthesis of some sesquiterpenes, is decribed.

E,E-Farnesyl acetate is treated with selenium dioxide to give E,E,E-12-hydroxy farnesyl acetate, which is transformed by DAST into E,E,E-12-fluorofarnesylacetate. The latter compound is hydrolyzed to E,E,E-12-fluorofarnesol.

The Reformatsky reaction of 6-methyl-5-hepten-2-one with ethyl bromofluoroacetate affords ethyl 2-fluoro-3-hydroxy-3, 7-dimethyl-6-octanoate. This ester is acetylated and eliminated to give ethyl (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dienoate, which is transformed to allyl bromide via allylic alcohol. The allyl bromide is treated with dianion of methyl acetate to give -keto ester. The $\beta$-keto ester is converted to diethyl phosphoryloxy compound. The conjugate addition of lithium dimethylcuprate to the latter compound gives fluoro ester, which is treated with DIBAL to afford E,Z-6-fluorofarnesol.

**Keywords** ☐ Inductive electron-withdrawing effect, Steric bulk, Antimetabolite, Mutagenesis, Fluoroterpene, Fluorosteroid, Cytostatic behavior, Cancerostatic activity, Regioisomer, Anti-phlogistic, Spinning band distillation.

Fluorine is the only element which can replace hydrogen without notable steric consequences.

In contrast to their similarity in size, hydrogen and fluorine are quite different in their reactivities. The high effective density of positive charge in the nucleus and the tendency to complete its valence shell render fluorine strongly electronegative. Attached to a reaction center it proves to be a moderately good leaving group. Placed in the vicinity of a reaction center, it may substantially influence reaction rates due to its inductive electron withdrawing effect.

The similarity of steric bulk and the dissimilarity of chemical behavior enable many fluorinated compounds to act as antimetabolites with respect to their corresponding halogen-free natural products. A typical example is given by fluoroacetic acid (1).

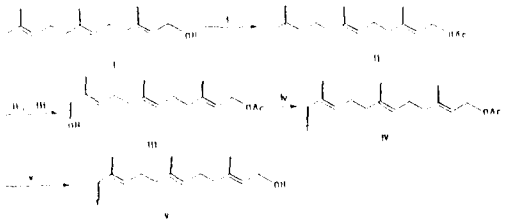
Once the principle of "antimetabolite formation by introduction of fluorine" had been recognized, it was tempting to apply it to chemotherapy. With this idea in mind Heidelberger, Duschinsky *et al.* synthesized 5-fluorouracil and its derivatives (2).

5-Fluorouracil was found to be incorporated in place of uracil into RNA of bacterial and mammalian cells as well as that of viruses causing mutagenesis, transcription errors and other defects. 5-Fluorouracil and its derivatives belong to the few drugs which are successfully employed in cancer treatment.

A number of fluoroterpenes were prepared to study their cytostatic behavior. Their natural halogen-free analogs are known as intermediates of steroid biosynthesis (3, 4), the key compound of which is epoxysqualene. Several steroid families descend from this oxirane. Besides cancerostatic activity, fluoroterpenes produced *in vivo* may exhibit other pharmaceutical effects, many fluorosteroids are known to be powerful drugs with anti-inflammatory, anti-phlogistic, anti-allergic, glucocorticoidal and anabolic properties (5).

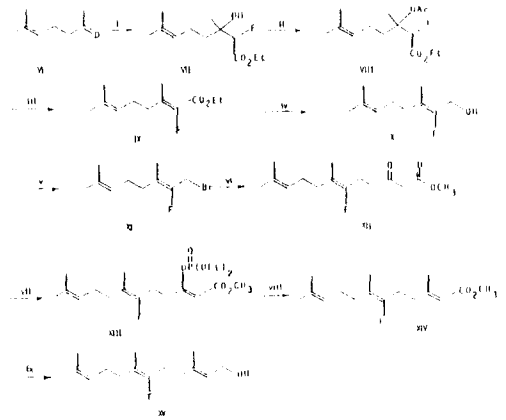
In addition to these pharmaceutical effects, fluorine-containing compounds have some advantages in detecting and identifying metabolic intermediates present in low concentrations.

In order to examine these hypotheses, E,E,E-12-fluoro-farnesol and E,Z-6-fluorofarnesol were synthesized (scheme 1 and scheme 2). These compound are used in order to investigate the tagging and metabolic blocking capabilities of fluorinated analogues of normal biological substrates by



i, $Ac_2O$, pyridine, ii, $SeO_2$(EtOH) iii, $NaBH_4$ iv, DAST($CCl_3F$) V, $K_2CO_3$(MeOH)

**Scheme.1**



i, $FBrCHCO_2Et$, $Zn(I_2)$ ii, $AC_2O$, Pyridine, TEA iii, EtONa(EtOH) iv, DIBAL(benzene) v, $PBr_3$(hexane)

vi,  vii, NaH, Cl-P(OEt)$_2$ ($Et_2O$) viii, $Me_2CuLi(Et_2O)$ ix, DIBAL($Et_2O$)

**Scheme.2**

studying the biosynthesis of cyclonerodiol from farnesyl pyrophosphate in the fungus *Gibberelle funjikuroi*.

## EXPERIMENTAL METHODS

All glasswares were thoroughly dried in a drying oven and cooled down under a stream of dry nitrogen just prior to use.

Most of the reagents utilized in syntheses were Aldrich products. There were further purified by distillation when necessary.

Ether was dried with excess lithium aluminum hydride, distilled undedr nitrogen, and stored over 4Å molecular sieve in a flask equipped with a rubber septum inlet.

Zinc was activated by washing several times with 5% HCl, $H_2O$, methanol and ether followed by drying with drying pistol.

DAST (Diethylaminosulfur trifluoride) was prepared as followings (6). A solution of 29g (200 mmol) of diethylaminotrimethylsilane in 20 m*l* of $CCl_3F$ was added dropwise to a solution of 12.5 m*l* (measured at −78℃, 269 mmol) of $SF_4$ in 60 m*l* of $CCl_3F$ at −78℃. The reaction mixture was warmed to RT. The solvent and by-product, fluorotrimethylsilane were distilled into a well-cooled receiver by warming the reaction mixture gently to 45℃ by means of a heating mantle. The dark-brown residual liquid was transferred and distilled at reduced pressure to give 26.2g (81.4%) of DAST as a light yellow liquid (bp 46-47℃ (10 mm.)). This product was stored in an inert plastic bottle.

Proton NMR spectra were recorded on Varian EM-360 spectrometer and the data were given in $\delta$ units downfield from tetramethylsilane. NMR spectra were obtained in $CDCl_3$. Infrared spectra were taken on Perkin-Elmer Model 337 spectrometer. All absorbances were reported in wave numbers ($cm^{-1}$). Gas chromatogram was recorded using Varian Model…3700 instrument equipped with Hewlett Packard Model 5830 digital integrator.

Thin layer chromatography was carried out with Merck, kiesel gel 60, PF 254 and chromatogram was visualized by mineral ultraviolet lamp. Column chromatography was performed with Merck kiesel gel 230-400 ASTM mesh.

3, 7, 11-***Trimethyldodeca*-2, 6, 10 *(E,E)*-*trien*-1-*ol (E,E-Farnesol)*** (***I***)

Commercial farnesol (Fluka AG.) available as a mixture of isomer (10% nerolidol, 54% Z,E-farnesol, 36% E,E,-farnesol) was separated by fractional distillation with spining band column (7). The separation was monitored by GC. using a 5% Carbowax Column, T. 180℃ ; $t_R$ 5.2 min. for nerolidol, 7 min. for Z,E-farnesol and 7.8 min. for E,E-farnesol.

***E,E-Farnesyl acetate*** (***II***)

A solution of 4g (180 mmol) of E,E-farnesol in 8 m*l* of anhydrous pyridine was treated with 8 m*l* of acetic anhydride. The resulting solution was stirred for 19 hr. at RT. The solution was poured into ice-$H_2O$ and extracted with $CHCl_3$. The organic extracts were washed with cold 5% aq. $H_2SO_4$ solution, sat'd $NaHCO_3$ solution and brine two times, respectively. The organic layer was dried over anhydrous $MgSO_4$ and condensed at reduced pressure. The residue was chromatographed on the silica gel column. Elution with hexane: EtOAc (9 : 1) gave 4.57g of E,E-farnesyl acetate (yield, 96%).

IR $\nu_{max}$ $cm^{-1}$ : 1650, 1725 ; NMR($CDCl_3$, TMS) $\delta$ 1.6 and 1.7(s, 12H), 2.0(s, 3H), 2.1(br.s, 8H), 4.62(d, J=7, 2H), 5.3(m, 3H).

***E,E,E*-12-*Hydroxy farnesyl acetate*** (***III***)

635 mg of $SeO_2$ (5.72 mmol) was added to 3g of

E,E-farnesyl acetate (11.4 mmol) in 95% EtOH, and the solution brought to reflux for 1.5 hr. The initial fine red precipitate turned to coarse and black during the course of reaction. After cooling to 10℃, it was filtered through celite. The EtOH was evaporated under vacuum, leaving an orange yellow oil which was dissolved in ether. The solution was filtered through a small amount of silica gel, washed with $H_2O$, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and condensed *in vacuo* to give 3.15g of residue. 215mg of $NaBH_4$ was added to the EtOH solution of this residue. The resulting mixture was stirred under the atmosphere of Ar for 18 hr. at RT. The reaction was quenched by the addition of 5% $H_2SO_4$ solution and condensed *in vacuo*. The residue was dissolved in $Et_2O$. The ether solution was washed with satd. $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$ filtered and condensed under reduced pressure to afford 3 g of an orange yellow oil. This crude product was chromatographed on the silica gel column. Elution with hexane: EtOAc (5 : 2) gave 795mg of E,E,E-12-hydroxy farnesyl acetate (25%), 223mg of E,E-farnesyl acetate (7%), and 159mg of E,E-8-hydroxy farnesyl acetate (5%).

IR $\nu_{max}$ $cm^{-1}$ : 3550, 1725, 1650; NMR($CDCl_3$, TMS) $\delta$ 1.65(s, 9H), 2.05(s, 11H), 2.8(s, 1H), 3.96(s, 2H), 4.62(d, J=7, 2H), 5.3(m, 3H).

***E,E,E*-12-*Fluorofarnesyl acetate* (*IV*)**

A solution of 560mg(2 mmol) of E,E,E-12-hydroxy farnesyl acetate in 20m*l* of $CCl_3F$ was slowly added to a solution of 250mg(2 mmol) of DAST in 5m*l* of $CCl_3F$ cooled to −78℃. The reaction mixture was warmed to RT. and mixed with cold water. The etheral layer was separated, washed with $H_2O$. It was dried over anhydrous $MgSO_4$ and condensed at reduced pressure. The residue was chromatographed on the silica gel column. Elution with hexane: EtOAc (9 : 1) gave 292mg of E,E,E-12-Fluorofarnesyl acetate (yield, 52%).

IR $\nu_{max}$ $cm^{-1}$ : 1025, 1365, 1450, 1725; NMR($CDCl_3$, TMS) $\delta$ 1.65(s, 9H), 2.05(s, 11H), 4.62(d, J=7, 2H), 4.93(d, J=46.8, 2H), 5.3(m, 3H).

***E,E,E*-12-*Fluorofarnesol* (*V*)**

A solution of 167mg(0.59 mmol) of E,E,E-12-fluorofarnesyl acetate in 15m*l* of MeOH was stirred with 179mg(1.30 mmol) of $K_2CO_3$ for 10 min at RT. before addition of 60m*l* of $Et_2O$ and 20m*l* of saturated $NH_4Cl$ solution. The organic layer was separated and the aqueous layer was extracted with $Et_2O$. The combined $Et_2O$ fractions were washed with $H_2O$ and saturated $Na_2CO_3$ soln. and dried over anhydrous $MgSO_4$. Solvent was removed at reduced pressure to give 121mg of E,E,E-12-Fluorofarnesol (yield, 85%).

IR $\nu_{max}$ $cm^{-1}$ : 1080, 1330, 1380, 3200~3615; NMR($CDCl_3$, TMS) $\delta$ 1.52(br. s, 1H), 1.68(s, 6H), 1.72(s, 3H), 2.05(s, 8H), 4.16(d, J=7, 2H), 4.91(d, J=47, 2H), 5.3(m, 2H), 5.65(m, 1H).

***Ethyl* 2-*fluoro*-3-*hydroxy*-3, 7-*dimethyl*-6-*octenoate* (*VII*)**

2.78g (22 mmol) of 6-methyl-5-hepten-2-one (VI) and 3.7g (20 mmol) of ethyl bromofluoroacetate were dissolved in 60m*l* of a 4 : 1 mixture of benzene and $Et_2O$ 10m*l* of the above solution was added to 2.6g (40 mmol) of activatied zinc and refluxed. A small crystal of $I_2$ was added. After starting the reaction, 50m*l* of the above solution was slowly added under reflux over a period of 1 hr. Then it was refluxed for an additional 1 hr. The reaction mixture was cooled to RT and cooled further with the use of ice-bath. 25m*l* of 10% $H_2SO_4$ solution was added and stirred until excess zinc is dissolved. Then it was extracted with $Et_2O$ and washed with 5% $H_2SO_4$ solution saturated $NaHCO_3$ solution (2×) and saturated NaCl solution. It was dried over anhydrous $MgSO_4$ and condensed at reduced pressure. The residue was chromatographed on the silica gel column. Elution with hexane: EtOAc (7 : 1) gave 3.79g of ethyl-2-fluoro-3-hydroxy-3, 7-dimethyl-6-octenoate (yield, 82%).

IR $\nu_{max}$ $cm^{-1}$ : 1720, 1760, 3520, 3590; NMR($CDCl_3$, TMS) $\delta$ 1.3(t, J=7, 3H), 1.5(d, J=4.3, 3H), 1.58(s, 3H), 2.13(m, 4H), 3.2(br. s, 1H), 4.25(q, J=7, 2H), 5.1(m, 1H), 5.2(d, J=47, 1H).

***Ethyl* 3-*acetoxy*-2-*Fluoro*-3, 7-*dimethyl*-6-*octenoate* (*VIII*)**

A solution of 444mg(1.63 mmol) of ethyl 2-fluoro-3-hydroxy-3, 7-dimethyl-6-octenoate in 1m*l* of anhydrous pyridine, was treated with 1m*l* of acetic anhydride and 1m*l* of triethyl amine. The resulting soln. was stirred for 18 hr. at RT. The solution was extracted with ether. The organic extracts were washed with 5% cold $H_2SO_4$ solution, saturated $NaHCO_3$ solution and brine two times, respectively. The organic layer was dried over anhydrous $MgSO_4$ and condensed at reduced pressure. The residue was chromatographed on the silica gel column. Elution with hexane: EtOAc (9 : 1) gave 483mg of ethyl 3-acetoxy-2-fluoro-3, 7-dimethyl-6-octenoate (yield, 92%).

IR $\nu_{max}$ $cm^{-1}$ : 1770, 1740, 1665; NMR($CDCl_3$, TMS) $\delta$ 1.3(t, J=7, 3H), 1.5(d, J=4.3, 3H), 1.58(s, 3H), 1.65(s, 3H), 2.2(s, 3H), 2.13(m, 4H), 4.25(q, J=7, 2H), 5.1(m, 1H), 5.25(d, J=47, 1H).

***Ethyl (Z)*** 2-***fluoro***-3, 7-***dimethylocta***-2, 6-***dienoate*** (***IX***)

In a 2 necked round bottomed flask, 166 mg of Na was placed under the atmosphere of Ar. Then 18 m*l* of anhydrous EtOH was added and heated slightly untill all the Na was dissolved. 820 mg of ethyl 3-acetoxy-2-fluoro-3, 7-dimethyl-6-octenoate was dissolved in 30 m*l* of anhydrous ether. To this etheral solution, 4 m*l* of the above Na ethanoic solution in 10 m*l* of ether was added slowly. The resulting solution was stirred for 2 hr. at RT. 100 mg of $NH_4Cl$ was added and stirred for 20 min. The reaction mixture was filtered through celite, dried over anhydrous $MgSO_4$ and condensed at reduced pressure. The residue was chromatographed on the silica gel column. Elution with hexane: EtOAc (9 : 1) gave 544 mg of mixture of ethyl (E) and (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dienoate. This mixture was separated with TLC (eluent, hexane: EtOAc (97 : 3), 2 developments). 275 mg (43%) of ethyl (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dienoate and 243 mg (38%) of ethyl (E)-2-fluoro-3, 7-dimethylocta-2, 6-dienoate were obtained.

IR $\nu_{max}$ $cm^{-1}$ : 1655, 1725, 1740, 1770 ; NMR($CDCl_3$, TMS) $\delta$ 1.3(t, J=7, 3H), 1.58(s, 3H), 1.65(s 3H), 2.07(d, J=3.4, 3H), 2.19(m, 4H), 4.25(q, J=7, 2H), 5.08(m, 1H).

***(Z)***-2-***Fluoro***-3, 7-***dimethylocta***-2, 6-***dien***-1-***ol*** (***X***)

A solution of 50 mg (0.23 mmol) of ethyl(Z) 2-fluoro-3, 7-dimethylocta-2, 6-dienoate in 3 m*l* of dry benzene was cooled to 0℃ under the atmosphere of Ar before addition of 1 m*l* of DIBAL (1 m*l* in hexane). The resulting mixture was stirred for 2 hr. at 0℃ before addition of 0.2 m*l* of MeOH. The cooling bath was removed, and it was stirred for 20 min at RT. The reaction mixture was treated with 0.5 N HCl solution until the aqueous layer turned clear. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and condensed at reduced pressure to give 40 mg of (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dien-1-ol (yield, 99.6%). The product was pure enough for the next reaction.

IR $\nu_{max}$ $cm^{-1}$ : 3620 ; NMR($CDCl_3$, TMS) $\delta$ 1.58(s, 3H), 1.67(s, 3H), 1.73(d, J=3.4, 3H), 1.97—2.15(m, 4H), 3.2(br. s, 1H), 4.92(d, J=22, 2H), 5.08(m, 1H).

***(Z)***-2-***Fluoro***-3, 7-***dimethylocta***-2, 6-***dien***-1-***bromide*** (***XI***)

12 $\mu$*l* of $PBr_3$ was added to a well stirred solution of 40 mg of (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dien-1-ol in 2 m*l* of anhydrous hexane at 0℃ under the atmosphere of Ar. The mixture was stirred at 0℃ for 20 min. and then three drops of MeOH were added. The resulting mixture was washed with cold saturated $NaHCO_3$ solution and cold brine. It was dried over anhydrous $MgSO_4$ and condensed at reduced pressure to give 48 mg of (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dien-1-bromide. It was used directly for the next reaction with out purification (yield, 82%).

NMR($CDCl_3$, TMS) $\delta$ 1.58(s, 3H), 1.67(s, 3H), 1.73(d, J=3.4, 3H), 1.97-2.15(m, 4H), 4.6(d, J=22, 2H), 5.08(m, 1H).

***Methyl*** (***6Z***) 6-***fluoro***-7, 11-***dimethyl***-3-***oxododeca***-6, 10-***dienoate*** (***XII***)

The dianion of methyl acetoacetate (232 mg, 2 mmol) in THF (5 m*l*) was prepared (8, 9) and treated with (Z)-2-fluoro-3, 7-dimethylocta-2, 6-dien-1-bromide (234 mg 1 mmol) at 0℃ and the yellow suspension formed was stirred for 1 hr. at 0℃ and then poured into 10 m*l* ice-cold satd. $NH_4Cl$ solution. The aqueous phase was extracted with $Et_2O$.

The combined organic solution was washed with brine and dried over anhydrous $MgSO_4$. It was condensed under vacuum to give 260 mg of crude product. This crude product was chromatographed on the silica gel column. Elution with hexane: EtOAc (9 : 1) gave 243 mg of methyl (6Z)-6-fluoro-7, 11-dimethyl-3-oxododeca-6, 10-dienoate (yield, 90%).

IR $\nu_{max}$ $cm^{-1}$ : 1630, 1650, 1715, 1745 ; NMR($CDCl_3$, TMS) $\delta$ 1.60(s, 3H), 1.67(s, 3H), 1.9(d, J=3.4, 3H), 1.8-2.3(m, 4H), 2.3-2.6(m, 4H), 3.38(s 2H), 3.65(s, 3H), 5.1(m, 1H).

***Methyl*** (***2Z, 6Z***) 3-***(diethylphosphoryloxy)***-6-***fluoro***-7, 11-***dimethyldodeca***-2, 6, 10-***trienoate*** (***XIII***)

To a stirred suspension of 15 mg (0.31 mmol) of NaH in dry $Et_2O$, kept under a dry $N_2$ and cooled in an ice-bath, was added a solution of 60 mg (0.22 mmol) of methyl (6Z) 6-fluoro-7, 11-dimethyl-3-oxododeca-6, 10-dienoate in $Et_2O$. After 20 min. at 0℃, 54 mg (0.31 mmol) of diethyl chlorophosphate was introduced and stirring was continued for 2 hr. at 0℃. The reaction mixture was stirred with excess of solid $NH_4Cl$ for 20 min. filtered through celite, and the filtrate was concentrated in vacuo to give 85.4 mg of methyl (2Z, 6Z)-3-(diethylphosphoryloxy)-6-fluoro-7, 11-dimethyldodeca-2, 6, 10-trienoate (yield, 95%).

IR $\nu_{max}$ $cm^{-1}$ : 1030, 1280, 1670, 1725 ; NMR($CDCl_3$, TMS) $\delta$ 1.35(t, J=7, 6H), 1.6(s, 3H), 1.67(s, 3H), 1.9(d, J=3.4, 3H), 1.8-2.3(m, 4H), 2.3-2.6(m, 4H), 3.65(s, 3H), 4.23(q, J=7, 4H), 5.1(m, 1H), 5.3(s, 1H).

***Methyl* (2*E*, 6*Z*) 6-*fluoro*-3, 7, 11-*trimethyldodeca*-2, 6, 10-*trienoate* (*XIV*)**

20.34 mg (0.92 mmol) of MeLi in $Et_2O$, was added dropwise to a stirred suspension of 88.13 mg (0.46 mmol) of CuI in dry $Et_2O$ at 0℃ and under a dry $N_2$. To the resulting light tan soln., cooled at −78℃, was added 85.4 mg (0.21 mmol) of methyl (2Z, 6Z) 3-(diethylphosphoryloxy) -6-fluoro-7, 11-dimethyldodeca-2, 6, 10-trienoate in 2 ml $Et_2O$. The resulting orange-yellow suspension was stirred at −78℃ for 2 hr. and then at −47℃ for 1 hr. The mixture turned dark purple. The mixture was poured into an ice-cold mixture of 50% aqueous $NH_4Cl$ and cond. $NH_4$ OH, and the aqueous phase was extracted with $Et_2$ O. The combined ether extracts were washed with brine, dried over $MgSO_4$ and then concentrated under reduced pressure to give 53 mg of methyl (2 E, 6Z) 6-fluoro-3, 7, 11-trimethyldodeca-2, 6, 10-trienoate (yield, 95%).

IR $\nu_{max}$ $cm^{-1}$ : 1155, 1650, 1715; NMR($CDCl_3$, TMS) $\delta$ 1.6(s, 3H), 1.67(s, 3H), 1.9(d, J=3.4, 3H), 2.0-2.5(m, 8H), 2.15(d, J=1.5, 3H), 3.65(s, 3H), 5.1(m, 1H), 5.62(br. s, 1H).

***E, Z*-6-*Fluorofarnesol* (*XV*)**

To a solution of 53 mg (0.2 mmol) of methyl (2 E, 6Z) 6-fluoro-3, 7, 11-triethyldodeca-2, 6, 10-trienoate in dry $Et_2O$ (3 ml), cooled at −23℃ and kept under $N_2$, was added 0.6 ml (0.6 mmol) of DIBAL (1M in hexane). The resulting mixture was stirred for 2 hr. at −23℃ and then quenched with 1 ml of MeOH. The cooling bath was removed, and after 20 min. the mixture was treated with 10% HCl until the aqueous layer turned clear. The $Et_2O$ layer was washed with brine, dried over anhydrous $MgSO_4$ and condensed under vacuum. This crude product was purified with TLC (eluent, hexane: EtOAc (5 : 1), 2 developments). 43.7 mg of pure product was obtained (yield, 92%).

IR $\nu_{max}$ $cm^{-1}$ : 1440, 1665, 3500, 3650; NMR($CDCl_3$, TMS) $\delta$ 1.6(s, 6H), 1.66(s, 3H), 1.9(d, J=3.4, 3H), 2.0-2.7(m, 8H), 4.2(d, J=7, 2H), 4.9-5.5(m, 2H).

## RESULTS AND DISCUSSION

The oxidation of E,E-farnesyl acetate (II) with $SeO_2$ in refluxing EtOH (10, 11) gave complicated mixture including corresponding aldehyde of desired product. Therefore, $NaBH_4$ reduction of the reaction mixture (II) was followed. By treating E,E-farnesyl acetate (II) with $SeO_2$ in refluxing EtOH and followed $NaBH_4$ reduction, E,E,E 12-hydroxy farnesyl acetate (III) was obtained in 25% yield along with regioisomer, E,E-8 hydroxy farnesyl acetate (5%), and recovered E,E -farnesyl acetate (7%). It was found that 2.5 hr. refluxing in EtOH was the best condition by careful monitoring of reaction conditions.

A modified procedure, developed by Umbreit and Sharpless (12) involving t-BuOH and a catalytic, or stoichiometric amout of $SeO_2$ was employed but the result was almost the same as usual $SeO_2$ oxidation.

The regiochemistry of the hydroxy group in the structures E,E,E-12-hydroxy farnesyl acetate (III) and E,E-8-hydroxy farnesyl acetate was established by analysis of their proton NMR data. The proton NMR spectrum of E,E,E-12-hydroxy farnesyl acetate (in $CDCl_3$) (III) showed absorptions at 1.65(s, 3H), 3.96(s, 2H), and 5.3(m, 1H), which were ascribed to protons at C-13, C-12 and C-10, respectively. Comparison of these data with those reported for the analogous allylic alcohol (E and Z) (11). The regioisomer, E,E -8-hydroxy farnesyl acetate exhibited a one-proton triplet (J=7 Hz) at 4.03 and a one-proton multiplet at 5.35 in its proton NMR spectrum, which were consistent with absorptions at C-8 and C-6 in the suggested structure.

The acetylation of ethyl 2-floro-3-hydroxy-3, 7-dimethyl-6-octenoate (VII) with acetic anhydride and pyridine (13) gave unsatisfactory results. A modified procedure (14) involving acetic anhydride and catalytic amount of triethyamine was then employed. By this procedure, ethyl 2-fluoro-3-hydroxy-3, 7-dimethyl-6-octenoate VII) was transformed into ethyl 3-acetoxy-2-fluoro -3, 7-dimethyl-6-octenoate (VIII) in 92% yield.

The dehydroacetoxylation of ethyl 3-acetoxy -2-fluoro3, 7-dimethyl-6-octenoate (VIII) with NaOEt gave a mixture of E and Z ethyl 2-fluoro -3, 7-dimethylocta-2, 6-dienoate which can't be separated easily (E:Z≒38 : 43).

In contrast to ethyl 2-fluoro-3, 7-dimethylocta -2, 6-dienoate, the following product, E and Z -2-fluoro-3, 7-dimethylocta-2, 6-dien-1-ol were separated with column chromatography easily.

In conclusion, E,E,E-12-fluorofarnesol and E,Z -6-fluorofarnesol were synthesized from commercially available starting materials for the study of biosynthesis of cyclonerodiol and cantharidin.

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