Acetyltrimethylsilane, Trifluoromethyltrimethylsilane, and Prenyl Esters: A Three-Component System for the Synthesis of *gem*-Difluoroanalogues of Monoterpenes

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The preparation of 3,3-difluoro-6-methylhept-5-en-2-one **1**, a key intermediate for the synthesis of 4,4-difluoroterpenes, and applications in linalool and geraniol series are described. The process involves 1,1-difluoro-2-trimethylsilyoxypropene, an enol silyl ether prepared from acetyltrimethylsilane and trifluoromethyltrimethylsilane, and its reaction in situ with prenyl benzoate, under catalysis by trimethylsilyl trifluoromethanesulfonate. Optimized conditions leading to either the desired enol silyl ether or the unprecedented methyl(trifluoromethyl)trimethylsilyl carbinol **4** have been achieved. The prenylation of the enol silyl ether gives a 9/1 mixture of regioisomers, in favor of the expected ketone **1**. Treatment of **1** with vinylmagnesium bromide leads to (±)-4,4-difluorolinalool **7**. Reaction with the lithium enolate of ethyl diethylphosphonoacetate, and then LAH reduction, converts **1** to 4,4-difluorogeraniol **11**, with complete stereoselectivity.

Introduction

The ability of fluorine to modify and/or enhance the biological properties of fluoro-substituted compounds has prompted organic chemists to develop selective methods of introduction of fluorine or fluorinated groups.[1] The field of terpenes is of particular interest since these compounds are involved in numerous aspects from bioorganic chemistry (steroids, pheromones, ...) to industrial chemistry (essential oils, flavors, ...). Various fluorinated terpenes have been reported. Often these derivatives were synthesized in order to compare their properties with those of the parent compound, mainly in the fields of pheromones,[2] flavors.[3] Other fluorinated terpene analogues were synthesized with the aim of studying biochemical mechanisms,[4] as for example to demonstrate the electrophilic character of the prenyl transfer processes by carbocation destabilizing ability of β-fluorine.[4b] On the other hand, regioselective cascade cyclization of polyenes was carried out taking advantage of the carbocation stabilizing effect of α-fluorine.[5] The fluorinated monoterpene analogues synthesized so far were substituted on C-2[6] or on the methyl group bonded to C-3[2a,3b,7,8] or C-7.[2c]

Our recent findings about the one-pot synthesis of α,α-difluorocarbonyl compounds from acylsilanes, trifluoromethyltrimethylsilane (TFMTMS) and electrophilic substrates via a difluoroenol silyl ether,[9] prompted us to apply this strategy to the synthesis of *gem*-difluoro analogues of terpenes. After our recent paper in the sesquiterpene series,[10] we report here the synthesis of 3,3-difluoro-6-methylhept-5-en-2-one **1**, the difluoro analogue of a key intermediate[11] in monoterpene synthesis, and its conversion into the corresponding difluoro linalool and difluorogeraniol.

Results and Discussion

The strategy adopted is depicted in Scheme 1. It consists of the reaction of 1,1-difluoro-2-trimethylsilyloxypropene **2**, prepared in situ from acetyltrimethylsilane **3** and TFMTMS under fluoride initiation,[12] with a prenyl

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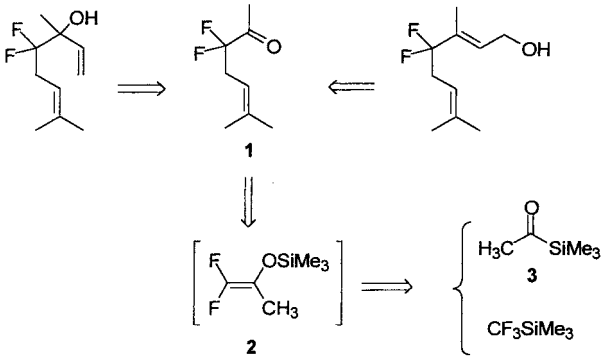
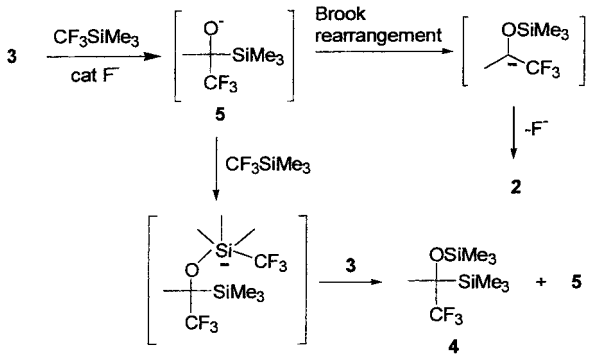
Scheme 1



Scheme 2

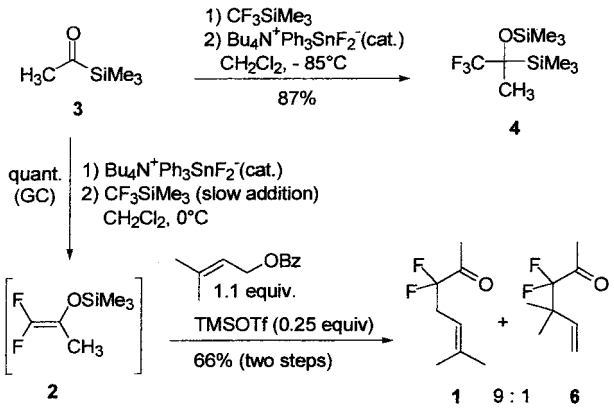


donor activated by a Lewis acid. To develop valuable synthesis of difluoroterpenes, we needed (i) an efficient preparation of **2**, (ii) an effective coupling of **2**, in the same pot, with the prenyl donor, and (iii) an effective one- or two-step conversion of the difluoroketone **1** into the targeted terpenes. These different aspects are successively developed in the following.

Optimized Conditions for the Preparation of 1,1-Difluoro-2-trimethylsilyloxypropene 2. We first applied to **3** the reaction conditions previously used in this laboratory, except for a lower reaction temperature, owing to the volatility of reactants and products. The first attempts failed to give both a high and reproducible yield of **2**. Lowering the reaction temperature allowed us in fact to isolate the addition compound: the trimethylsilyl ether of methyl(trifluoromethyl)trimethylsilyl carbinol **4**. The formation of this compound means that the silicon chain transfer reaction at the oxygen of the adduct **5,** a bimolecular process, competes with the Brook rearrangement, a monomolecular one (Scheme 2). Indeed, it was easy to favor either of the two reaction pathways: a slow addition, at 0 °C, of TFMTMS to a dichloromethane solution of **3** containing a catalytic amount of the fluoride initiator yielded quantitatively (GC) the silyl enol ether **2**, whereas addition of the fluoride initiator to a solution of **3** and TFMTMS cooled to −80 °C gave selectively the silyl ether **4** (87% isolated) (Scheme 3). For the first time the nucleophilic trifluoromethyl addition on an acylsilane allowed the effective trapping of the primary alcoholate adduct, giving the corresponding silyl(trifluoromethyl)-carbinol. Until now, the trapping of this type of alcoholates was only successful with the higher R_F homologues.[13] Owing to our experience in this chemistry,[9] it

(12) The choice of tetra-*n*-butylammonium difluorotriphenylstannate has been demonstrated to be crucial to avoid self-condensation of the silyl enol ether; see ref 9a.

Scheme 3



seems that the chain transfer reaction is very sensitive to the steric hindrance and that only a methyl group on the functionalized carbon allows a competing transfer of silicon at the oxygen.

Coupling of 2 with the Prenyl Donor. In a previous work,[10] we carried out the prenylation of aroylsilanes using zinc diiodide[14] (excess) or trimethylsilyl triflate (catalytic) as the activator and prenyl acetate as the prenyl donor. The application of these conditions to the prenylation of the difluoroenol silyl ether **2** either gave poor yield and/or induced problematic separation of the products. The polymerization of the acetate competes using ZnI_2. NMR monitoring of the reaction revealed a clean coupling under TMSOTf activation, but the excess of prenyl acetate proved to be difficult to separate from the coupling products. Substitution of prenyl benzoate for the corresponding acetate allowed easy isolation of the coupling products, provided that an adapted workup and solvent removal was applied.

Finally, the best result was obtained using the following conditions (see Experimental Section for more details): prenyl benzoate (1 equiv) and TMSOTf (0.25 equiv) were added to the dichloromethane solution of **2** cooled to −20 °C. The remaining part of prenyl benzoate was slowly added with a syringe pump and left to react until completion of the reaction (^{19}F NMR monitoring). After hydrolytic workup, the solvent and volatile products were transferred under vacuum in a liquid nitrogen cooled trap and the solvent was distilled under atmospheric pressure. This procedure allowed a clean isolation of a 9/1 mixture of the expected coupling product **1** and its regioisomer **6**, with an overall yield of 66% from the starting acetyltrimethylsilane **3** (Scheme 3). Because of its high volatility, **1** was characterized as its 2,4-dinitrophenylhydrazone derivative. The separation of the regioisomers **1** and **6** by distillation proved to be difficult. Therefore, we decided to carry the mixture through the next steps, hoping for an easier separation at a later stage.

Synthesis of (±)-4,4-Difluorolinalool. Difluorolinalool **7** was simply prepared by addition of vinylmagnesium bromide to the ketone **1** (containing 10% **6**). Pure **7**[15] (59%) was obtained after flash chromatography of the mixture containing the regioisomer adduct **8** (7% isolated) (Scheme 4).

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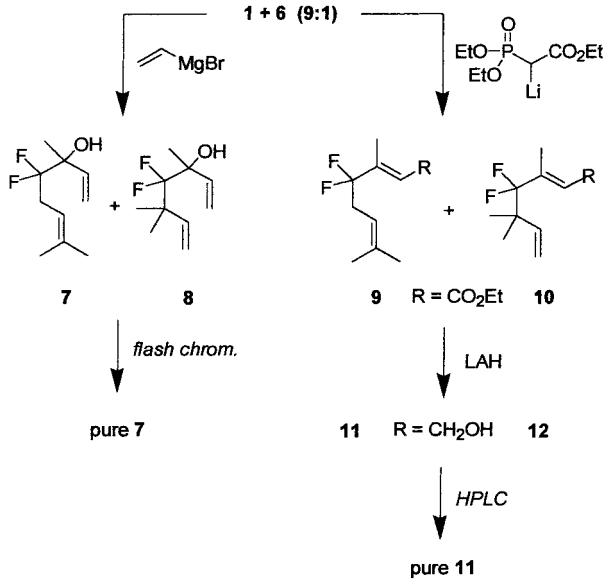
(15) The difluorolinalool **7** was fully characterized as its 3,5-dinitrobenzoate ester.

Scheme 4



Synthesis of 4,4-Difluorogeraniol. As already carried out with the hydrogenated analogue of **1**,[16] **1** + **6** (9/1) were converted into the nonseparable difluoro esters **9** + **10** (9/1) in 72% yield by a Wadsworth−Emmons reaction with the lithium enolate of ethyl diethylphosphonoacetate (Scheme 4). In contrast to the nonfluorinated and the C-3-fluoromethyl series, the reaction was completely stereoselective, giving exclusively the *E* isomer, probably because of a more effective thermodynamic control. The *E* configuration was determined according to the $^4J_{HF}$ coupling constant (1.5 Hz) of the vinylic hydrogen and to the absence of NOE on the vinylic methyl group after irradiation of the vinylic hydrogen.

Reduction of these esters with LAH gave the expected difluorogeraniol **11** contaminated with 10% of its regioisomer **12** (**11** + **12**: 75%). A pure sample of **11** was obtained by semipreparative HPLC on silica gel.

Compounds **7** and **11** have a pleasant odor, although olfactometric evaluation has not been performed.

Conclusion

Acetyltrimethylsilane and TFMTMS prove to be interesting reagents toward the synthesis of targeted *gem*-difluoro analogues of monoterpenes. The strategy, exemplified here with linalool and geraniol, consists of a three-component one-pot reaction sequence, followed by one (linalool) or two (geraniol) simple steps. 1,1-Difluoro-2-trimethylsilyloxypropene **2** and its coupling with prenyl benzoate leading to the difluoroheptenone **1** are the key intermediates and step. One drawback was the contamination of **1** with 10% of its regioisomer, which was easily overcome for linalool synthesis but induced further HPLC treatment for geraniol. Conversely, the olefination step of **1** led specifically to the configuration corresponding to geraniol.

Experimental Section[10]

Tetra-*n*-butylammonium difluorotriphenylstannate was prepared according to the reported procedure.[17] CF_3TMS was provided by Bayer Company (Leverkusen).

1,1,1-Trifluoro-2-trimethylsilyl-2-trimethylsilyloxypropane (4). To a solution of acetyltrimethylsilane (3 g, 25.8 mmol) and TFMTMS (5 mL, 33.8 mmol, 1.3 equiv) in dry CH_2Cl_2 (80 mL) at −85 °C under argon was added a solution of a catalytic amount of tetra-*n*-butylammonium difluorotriphenylstannate (830 mg, 1.3 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL). After 2 h of stirring at −85 °C, the temperature was allowed to rise to room temperature and the solvent was evaporated under reduced pressure. Compound **4** was purified by distillation (5.6 g, 87%). Colorless liquid; bp_{10} 46 °C;^{1}H NMR δ 0.10 (s, 9H), 0.15 (s, 9H), 1.40 (s, 3H); ^{19}F NMR δ −76.5 (s); ^{13}C NMR δ −3.7 (s), 2.2 (s), 18.5 (s), 71.0 (q, $^2J_{CF}$ = 31.5 Hz), 128.2 (q, J_{CF} = 283.5 Hz); IR (neat) 2961, 1148, 833 cm^{-1}; MS (CI with NH_3) *m*/*z* 259 (M + 1, 2), 239 (M − HF, 3), 166 (8), 164 (12), 90 (100).

One-Pot Prenylation Procedure. To a solution of acetyltrimethylsilane (13 g, 0.112 mol) and tetra-*n*-butylammonium difluorotriphenylstannate (3.7 g, 5.9 mmol, 0.05 equiv) in dry CH_2Cl_2 (400 mL) at 0 °C under argon and protected from light was added dropwise TFMTMS (23 mL, 0.156 mol, 1.39 equiv) in 20 min. After 15 min of stirring, another portion of tetra-*n*-butylammonium difluorotriphenylstannate (1 g, 1.6 mmol, 0.01 equiv) was added. The mixture was stirred for 45 min at room temperature, and the formation of the difluoroenoxysilane was monitored by GC. To this solution were then successively added at −20 °C a portion of 3,3-dimethylallylbenzoate (5 mL, 26.3 mmol, 0.23 equiv), TMSOTf (5 mL, 27.7 mmol, 0.25 equiv), and another portion of 3,3-dimethylallylbenzoate (18 mL, 94.7 mmol, 0.85 equiv) dropwise with a syringe pump (0.9 mL/min). After completion of the reaction (^{19}NMR monitoring), the solution was hydrolyzed with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$, and the volatile fraction was evaporated in vacuo (1 mm Hg) at 55 °C and collected in a liquid nitrogen trap. The solvent was evaporated at atmospheric pressure, and an inseparable 9:1 mixture of ketones **1** and **6** (12 g, 66%) was obtained after distillation (bp 100−110 °C).

3,3-Difluoro-6-methylhept-5-en-2-one (1). ^{1}H NMR δ 1.63 (d, $^4J_{HH}$ = 1.1 Hz, 3H), 1.63 (s, 3H), 2.30 (t, $^4J_{HF}$ = 1.9 Hz, 3H), 2.70 (td, $^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 7.6 Hz, 2H), 5.08 (tq, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, 1H); ^{19}F NMR δ −106.5 (t, $^3J_{HF}$ = 17.2 Hz); ^{13}C NMR δ 17.9, 20.5, 25.9, 31.9 (t, $^2J_{CF}$ = 23.6 Hz), 112.6 (t, $^3J_{CF}$ = 4.9 Hz), 117.5 (t, J_{CF} = 252.0 Hz), 138.5, 199.2 (t, $^2J_{CF}$ = 31.5 Hz); IR (neat) 2964, 2932, 1745, 1722, 1273 cm^{-1}; MS *m*/*z* 162 (M$^+$, 8), 144 (46), 142 (28), 127 (100).

3,3-Difluoro-4,4-dimethylhex-5-en-2-one (6). ^{1}H NMR δ 1.18 (t, $^4J_{HF}$ = 0.8 Hz, 6H), 2.27 (t, $^4J_{HF}$ = 1.9 Hz, 3H), 5.14 (d, $^3J_{HH}$ = 17.6 Hz, 1H), 5.19 (d, $^3J_{HH}$ = 10.7 Hz, 1H), 5.95 (dd, $^3J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 10.7 Hz, 1H), ^{19}F NMR δ −114.9 (s).

2,4-Dinitrophenylhydrazone Derivatives of 1 and 6. A mixture of difluoroketones **1** and **6** (300 mg, 1.85 mmol) and 2,4-dinitrophenylhydrazine (366 mg, 1.85 mmol) in EtOH (3 mL) and AcOH (0.02 mL) was refluxed for 5 h. Removal of the solvent under reduced pressure and purification by silica gel column chromatography (9:1 petroleum ether/AcOEt) gave a 9:1 mixture of hydrazones **1 DNPH** and **6 DNPH** (337 mg, 53%). Recrystallization in EtOH gave a pure sample of hydrazone **1 DNPH**.

3,3-Difluoro-6-methylhept-5-en-2-one 2,4-Dinitrophenylhydrazone (1 DNPH). Orange needles; mp 76 °C. ^{1}H NMR δ 1.70 (s, 3H), 1.76 (s, 3H), 2.16 (s, 3H), 2.98 (td, $^3J_{HF}$ = 15.3 Hz, $^3J_{HH}$ = 6.8 Hz, 2H), 5.22 (tm, $^3J_{HH}$ = 6.8 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 9.5 Hz, 1H), 8.38 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 2.5 Hz 1H), 9.13 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 11.09 (s, 1H); ^{19}F NMR δ −98.2 (t, $^3J_{HF}$ = 15.3 Hz); ^{13}C NMR δ 10.5, 18.1, 25.8, 32.2 (t, $^2J_{CF}$ = 24.6 Hz), 114.2 (t, $^3J_{CF}$ = 4.8 Hz), 116.6, 120.4 (t, J_{CF} = 239.3 Hz), 123.1, 130.1, 130.3, 137.0, 139.0, 144.6, 148.7 (t, J_{CF} = 34.1 Hz); IR (neat) 3318, 3310, 2984, 2925, 1616, 1590, 1335 cm^{-1}; MS *m*/*z* 342 (M$^+$, 8), 325 (8), 307 (100), 191 (18), 142 (22), 125 (34). Anal. Calcd for $C_{14}H_{16}O_4F_2N_4$: C, 49.12, H, 4.71, N, 16.37. Found: C, 48.95, H, 4.46, N, 16.15.

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3,3-Difluoro-4,4-dimethylhex-5-en-2-one 2,4-Dinitrophenylhydrazone (6 DNPH). ^{1}H NMR δ 1.25 (t, $^4J_{HF}$ = 2.2 Hz, 6H), 2.11 (s, 3H), 5.14 (d, $^3J_{HH}$ = 11.1 Hz, 1H), 5.20 (d, $^3J_{HH}$ = 17.5 Hz, 1H), 6.05 (dd, $^3J_{HH}$ = 17.5 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 9.5 Hz, 1H), 8.38 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 2.5 Hz 1H), 9.13 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 11.09 (s, 1H); ^{19}F NMR δ −108.0 (s).

Synthesis of Difluorolinalool 7. To a solution of a 9:1 mixture of ketones **1** and **6** (1.35 g, 8.3 mmol) in dry diethyl ether (15 mL) under argon was added, dropwise, at 0 °C, a solution of vinylmagnesium bromide (16.7 mL, 1 M in diethyl ether, 16.7 mmol). After stirring for 6 h at room temperature, the reaction was quenched with 1 M aqueous HCl and extracted with diethyl ether (3 × 50 mL). The organic layer was washed with brine and dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (7:3 petroleum ether/CH_2Cl_2) to give pure fractions of alcohols **8** (100 mg, 6%) and **7** (900 mg, 57%).

(±)-4,4-Difluoro-3,7-dimethylocta-1,6-dien-3-ol (7). Colorless liquid. ^{1}H NMR δ 1.39 (s, 3H) 1.62 (s, 3H), 1.76 (s, 3H), 2.41 (s, 1H), 2.63 (m, 2H), 5.24−5.27 (m, 2H), 5.47 (d, $^3J_{HH}$ = 17.2 Hz, 1H), 6.02 (dd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.7 Hz, 1H); ^{19}F NMR δ −111.4 (ddd, $^2J_{FF}$ = 247.0 Hz, $^3J_{HF}$ = 25.8 Hz, $^3J_{HF}$ = 10.7 Hz, 1F), −114.7 (ddd, $^2J_{FF}$ = 247.0 Hz, $^3J_{HF}$ = 27.2 Hz, $^3J_{HF}$ = 11.6 Hz, 1F); ^{13}C NMR δ 17.8, 21.8, 25.7, 30.5 (t, $^2J_{CF}$ = 24.6 Hz), 75.7 (t, $^2J_{CF}$ = 27.6 Hz), 114.4 (d, $^3J_{CF}$ = 3.9 Hz), 114.5, 123.8 (t, J_{CF} = 250 Hz), 136.0, 138.4 (d, $^3J_{CF}$ = 3.0 Hz); IR (neat) 3462, 2997, 2936, 1454, 1373, 1064 cm^{-1}; MS *m*/*z* 190 (M$^+$, 2), 172 (12), 152 (36), 150 (42), 137 (48), 135 (56), 71 (100).

(±)-4,4-Difluoro-3,5,5-trimethylhepta-1,6-dien-3-ol (8). Colorless liquid. ^{1}H NMR δ 1.21 (s, 3H) 1.23 (s, 3H), 1.35 (s, 3H), 2.14 (s, 1H), 5.02−5.18 (m, 3H), 5.38 (d, $^3J_{HH}$ = 17.1 Hz, 1H), 6.07 (dd, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 6.13 (dd, $^3J_{HH}$ = 17.9 Hz, $^3J_{HH}$ = 10.5 Hz, 1H);^{19}F NMR δ −113.4 (d, $^2J_{FF}$ = 255.6 Hz, 1F), −115.9 (d, $^2J_{FF}$ = 255.6 Hz, 1F); ^{13}C NMR δ 22.4 (t, $^3J_{CF}$ = 3.9 Hz), 23.4 (t, $^3J_{CF}$ = 4.9 Hz), 24.5 (t, $^3J_{CF}$ = 4.9 Hz), 29.6 (t, $^2J_{CF}$ = 23.6 Hz), 77.9 (dd, $^2J_{CF}$ = 29.5 Hz, $^2J_{CF}$ = 27.6 Hz), 112.9, 113.2, 123.4 (t, J_{CF} = 258 Hz), 140.4 (d, $^3J_{CF}$ = 4.9 Hz), 142.8 (t, $^3J_{CF}$ = 3.9 Hz); IR (neat) 3474, 2922, 2847, 1454, 1379, 1240 cm^{-1}; MS (CI with NH_3) *m*/*z* 208 (M + 18, 1), 162 (15), 144 (46), 127 (100).

(±)-2,2-Difluoro-1,5-dimethyl-1-vinylhex-4-enyl 3,5-Dinitrobenzoate (7 DNBz). To a solution of **7** (275 mg, 1.4 mmol) in pyridine (8 mL) was added 3,5-dinitrobenzoyl chloride (991 mg, 4.3 mmol), and the mixture was refluxed for 5 h. The reaction mixture was then poured in water (30 mL) and extracted with diethyl ether (4 × 30 mL). The organic layer was, successively, washed with 1 M aqueous HCl (20 mL), brine (15 mL), and a saturated $NaHCO_3$ aqueous solution (20 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (9:1 petroleum ether/ethyl acetate) and recrystallized from petroleum ether to give pure 3,5-dinitrobenzoate derivative **7 DNBz** (108 mg, 20%) as white needles: mp 73 °C. ^{1}H NMR δ 1.57 (s, 3H), 1.78 (d, $^4J_{HH}$ = 1.2 Hz, 3H), 1.92 (s, 3H), 2.76 (tm, $^3J_{HF}$ = 18.2 Hz, 2H), 5.31 (tm, $^3J_{HH}$ = 7.2 Hz, 1H), 5.46 (d, $^3J_{HH}$ = 17.5 Hz, 1H), 5.53 (d, $^3J_{HH}$ = 11.1 Hz, 1H), 6.04 (dd, $^3J_{HH}$ = 17.5 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 9.12 (d, $^4J_{HH}$ = 2.3 Hz, 2H), 9.24 (t, $^4J_{HH}$ = 2.3 Hz, 1H); ^{19}F NMR δ −112.3 (t, $^3J_{HF}$ = 18.2 Hz); ^{13}C NMR δ 16.8 (t, $^3J_{CF}$ = 3.9 Hz), 17.9, 25.9, 31.1 (t, $^2J_{CF}$ = 24.6 Hz), 86.2 (t, $^2J_{CF}$ = 27.5 Hz), 113.3 (t, $^3J_{CF}$ = 3.9 Hz), 119.5, 121.8 (t, J_{CF} = 251 Hz), 122.5, 129.4, 134.0 (t, $^3J_{CF}$ = 2 Hz), 134.3, 137.6, 148.7, 160.2; IR (neat) 3104, 2932, 1743, 1552, 1344 cm^{-1}; MS *m*/*z* 384 (M$^+$, 19), 364 (18), 332 (27), 245 (15), 195 (85), 149 (48), 111 (100). Anal. Calcd for $C_{17}H_{18}F_2N_2O_6$: C, 53.13, H, 4.72, N, 7.29. Found: C, 53.38, H, 4.37, N, 7.16.

Wadsworth−Emmons Olefination. To a solution of triethyl phosphonoacetate (12.3 mL 60 mmol) in dry THF (70 mL) at 0 °C under argon was added BuLi (25 mL, 2.5 M in hexane, 62.6 mmol) dropwise. After 45 min, a 9:1 mixture of ketones **1**, **6** (5 g, 30.9 mmol) was added dropwise and the mixture was stirred for 1 h at 0 °C and 18 h at room temperature. The reaction was quenched with water and extracted with diethyl ether (3 × 60 mL). The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (9:1 petroleum ether/CH_2Cl_2) to give an inseparable 9:1 mixture of esters **9** and **10** (4.3 g, 60%) as a colorless liquid.

(2*E*)-Ethyl 4,4-Difluoro-3,7-dimethylocta-2,6-dienoate (9). ^{1}H NMR δ 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.63 (s, 3H), 1.73 (s, 3H), 2.18 (d, $^4J_{HH}$ = 1.5 Hz, 3H), 2.67 (td, $^3J_{HF}$ = 16.4 Hz, $^3J_{HH}$ = 7.2 Hz, 2H), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 2H) 5.07 (tq, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 6.07 (q, $^4J_{HH}$ = 1.5 Hz, 1H); ^{19}F NMR δ −101.7 (t, $^3J_{HF}$ = 16.4 Hz); ^{13}C NMR δ 14.1, 17.9, 21.2, 25.7, 34.9 (t, $^2J_{CF}$ = 27.6 Hz), 60.3, 113.9, 118.7 (t, $^3J_{CF}$ = 8.8 Hz), 118.9, 121.9 (t, J_{CF} = 244.1 Hz), 137.3, 165.9; IR (neat) 2984, 2934, 1726, 1666, 1238 cm^{-1}; MS *m*/*z* 232 (M$^+$, 5), 212 (25), 187 (20), 164 (24), 139 (100). Anal. Calcd for $C_{12}H_{18}O_2F_2$: C, 62.05, H, 7.81. Found: C, 62.33, H, 7.70.

(2*E*)-Ethyl 4,4-Difluoro-3,5,5-trimethylhepta-2,6-dienoate (10). ^{1}H NMR δ 1.16 (s, 6H), 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.15 (d, $^4J_{HH}$ = 1.5 Hz, 3H), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 5.07 (d, $^3J_{HH}$ = 17.5 Hz, 1H), 5.14 (d, $^3J_{HH}$ = 11.0 Hz, 1H), 5.94 (dd, $^3J_{HH}$ = 17.5 Hz, $^3J_{HH}$ = 11.0 Hz, 1H), 5.98 (q, $^4J_{HH}$ = 1.5 Hz, 1H); ^{19}F NMR δ −108.4 (s); MS (CI with NH_3) *m*/*z* 250 (M + 18, 6), 213 (12), 195 (100), 167 (26), 151 (32).

Reduction of 9 and 10. To a solution of LAH (196 mg, 5.2 mmol) in dry diethyl ether (2 mL) under argon was added, dropwise, at room temperature, a solution of a 9:1 mixture of esters **9** and **10** (1.0 g, 4.3 mmol) in dry diethyl ether (5 mL). After stirring for 18 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (3 × 50 mL). The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (4:1 petroleum ether/ethyl acetate) to give an inseparable 9:1 mixture of alcools **11** and **12** (614 mg, 75%) as a colorless liquid. A pure sample of difluorogeraniol **11** (57 mg) was be obtained after separation of the mixture (110 mg) by HPLC with a Lichrosorb Si 60 (7 μm) column (99:1 hexanes/2-propanol elution).

(2*E*)-4,4-Difluoro-3,7-dimethylocta-2,6-dien-1-ol (11). Colorless liquid. ^{1}H NMR δ 1.63 (s, 3H), 1.73 (s, 6H), 2.47 (s, 1H), 2.66 (td, $^3J_{HF}$ = 15.7 Hz, $^3J_{HH}$ = 7.2 Hz, 2H), 4.36 (m, 2H), 5.10 (tm, $^3J_{HH}$ = 7.2 Hz 1H), 5.93 (tm, $^3J_{HH}$ = 6.1 Hz 1H); ^{19}F NMR δ −99.6 (t, $^3J_{HF}$ = 15.7 Hz); ^{13}C NMR δ 11.7, 17.9, 25.7, 34.8 (t, $^2J_{CF}$ = 27.6 Hz), 58.8, 114.7 (t, $^3J_{CF}$ = 5.0 Hz), 122.4 (t, J_{CF} = 241.1 Hz), 128.2 (t, $^3J_{CF}$ = 8.8 Hz), 132.7 (t, $^2J_{CF}$ = 25.6 Hz), 136.4; IR (neat) 3325, 2972, 2920, 2883, 1678, 1450 cm^{-1}; MS *m*/*z* 191 (M + 1, 5), 173 (22), 170 (50), 140 (95), 139 (100). Anal. Calcd for $C_{10}H_{16}OF_2$: C, 63.14, H, 8.48. Found: C, 63.30, H, 8.64.

(2*E*)-4,4-Difluoro-3,5,5-trimethylhepta-2,6-dien-1-ol (12). ^{1}H NMR δ 1.13 (s, 6H), 1.63 (s, 3H), 1.79 (s, 1H), 4.25 (m, 2H), 5.02−5.15 (m, 2H), 5.83 (tm, $^3J_{HH}$ = 6.1 Hz, 1H), 5.96 (dd, $^3J_{HH}$ = 17.5 Hz, $^3J_{HH}$ = 11.1 Hz, 1H); ^{19}F NMR δ −107.0 (s); MS (CI with NH_3) *m*/*z* 208 (M + 18, 1), 171 (4), 155 (100), 151 (64).

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