Synthesis of Fluorinated Analogues of Geraniol[1,2]

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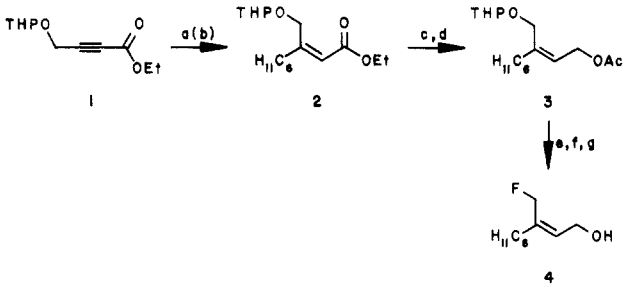
Syntheses of 3-(fluoromethyl)geraniol (4), 3-(difluoromethyl)geraniol (14), and 3-(trifluoromethyl)geraniol (20) are described. The key reaction in the routes to alcohols 4 and 20 which establishes the geranyl *Z* stereochemistry at the C(2)–C(3) double bond is the cis addition of (4-methylpent-3-en-1-yl)copper reagents to derivatives of ethyl 2-butynoate bearing appropriate functional groups at C(4). Attempts to prepare difluoromethyl alcohol 14 by similar routes were unsuccessful. However, the carbon skeleton of 14 was constructed by a Wittig condensation of 1,1-difluoro-6-methylhept-5-en-2-one (12) with triethyl phosphonoacetate in a reaction that yielded a 72:28 ratio of geranyl/neryl isomers.

Pronounced biological effects are usually seen when hydrogen atoms in a natural metabolite are replaced by fluorine.[4] This behavior is usually attributed to two properties of fluorine. First, the van der Waals radius of fluorine (~1.35 Å)[5] is only slightly larger than that of hydrogen (~1.2 Å). Thus, unlike other substitutions, the replacement of a hydrogen atom by fluorine does not introduce large steric perturbations which might interfere with binding interactions to an enzyme or a receptor. Second, fluorine is the most electronegative of the elements.[6] Because of its electron-withdrawing effect, fluorine may substantially alter the rate of a reaction when placed near the reaction center.[7] Such behavior is exemplified by the use of fluorinated analogues with depressed reactivities to reversibly inhibit prenyl transfer enzymes[8] or to increase the resistance of drugs to oxidative metabolism.[9] Fluorine is also a moderately good leaving group when located at a reaction center,[10] and an increasing number of analogues are being discovered which inhibit enzymes irreversibly by covalent attachment to nucleophilic functional groups in the active site.[11]

During the past several years, a variety of fluorinated terpenes have been synthesized as insecticides,[12,13] for studies of enzyme mechanisms,[8,14-18] and for pharmacological evaluation.[9] One of the major problems encountered in each instance is stereocontrol in the reactions used to introduce the trisubstituted double bond in the vicinity of the fluorine. Schlosser[4] recently reviewed procedures for replacing the olefinic hydrogen with fluorine and presented a procedure for achieving stereocontrol. However, adequate solutions have not been published for positioning fluorine at carbons adjacent to the double bond, where Wittig reactions involving methyl ketones are usually employed as a key step.[9,12-15,17-20] In most instances, approximately equal amounts of both stereoisomers are produced, and tedious chromatographic separations are often required to obtain pure compounds.

Scheme I.[a] Synthesis of 3-(Fluoromethyl)geraniol



1 2 3 4

[a] (a) $C_6H_{11}Cu$, −77 °C; (b) $(C_6H_{11})_2CuLi$, −77 °C; (c) $LiAlH_4$, −55 °C; (d) Ac_2O, pyridine; (e) PPTS, 55 °C; (f) $(Et_2N)(Me_2N)SF_2$, −65 °C; (g) K_2CO_3.

We present stereoselective procedures for preparing 3-(fluoromethyl)geraniol (4) and 3-(trifluoromethyl)geraniol (20) based on the cis addition of organocopper reagents to acetylenic esters reported by Siddall and co-workers during their synthesis of juvenile hormone.[21] Two approaches for synthesis of 2-(difluoromethyl)geraniol (14) from precursors used for the monofluoro analogue were unsuccessful, and we resorted to the traditional Wittig route for that compound.

Results and Discussion

3-(Fluoromethyl)geraniol (4). A stereoselective synthesis of 3-(fluoromethyl)geraniol (4) is presented in Scheme I. The key reaction is the conjugate addition of the 4-methylpent-3-en-1-yl moiety (C_6H_{11}) to acetylenic ester 1. This step establishes the correct stereochemistry

(1) Support of this research by the National Institutes of Health (Grant GM-21328) is gratefully acknowledged.

(2) Abbreviations used are as follows: Ac, acetate; Bn, benzyl; DAST, (diethylamino)sulfur trifluoride; IR, infrared; LC, liquid chromatography; NMR, nuclear magnetic resonance; PPTS, pyridinium *p*-toluenesulfonate; THP, tetrahydropyranyl; TLC, thin-layer chromatography; Me_4Si, tetramethylsilane.

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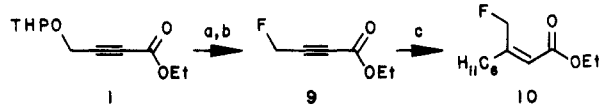
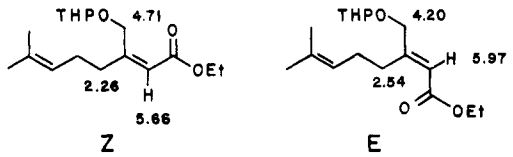
Scheme II.[a] Alternate Synthesis of 3-(Fluoromethyl)geraniol



[a] (a) PPTS, 60 °C; (b) DAST, −78 °C; (c) $C_6H_{11}Cu$.

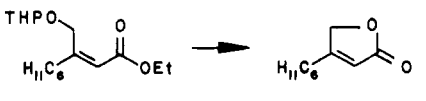
for the C(2)–C(3) double bond in ester **2** and affords a blocked hydroxymethyl group at C(3) that can later be converted to the corresponding alkyl fluoride. Two variations of the conjugate addition were studied. One was based on a report by Henrick and co-workers[22] of the stereospecific addition of butylcopper to methyl 2-butynoate in high yield and the other on use of the lithium dialkylcuprate.[21] In our hands, addition of (4-methyl-3-penten-1-yl)copper was stereospecific but gave a somewhat lower yield of the desired ester (50% after chromatography) than the corresponding lithium dialkylcopper reagent. In the latter case, a 95:5 ratio of *Z*/*E* double bond isomers was obtained at −77 °C. However, the compounds were readily separated by medium-pressure LC, and the desired geranyl derivative (**2**) was obtained in 70% yield.



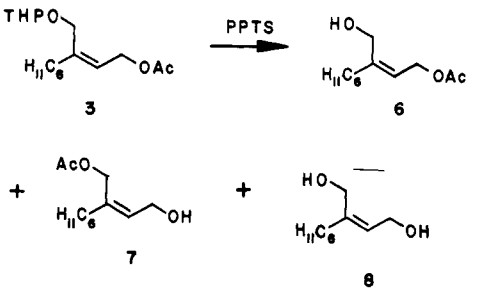
Initially the stereochemistry of the C(2)–C(3) double bond was established by comparing the chemical shifts of the protons at C(2), C(4), and the alkoxymethyl group. In each instance the protons at C(4) and on the alkoxymethyl carbon cis to the carbethoxy group are deshielded by 0.28 to 0.51 ppm relative to the shifts of the corresponding trans orientation.[23] In addition, the olefinic proton at C(2) in the *Z* isomer (**2**) trans to the alkoxymethyl moiety at C(3) appears 0.31 ppm upfield from the cis-oriented olefinic proton in the *E* isomer.

An unambiguous assignment of stereochemistry was obtained by a nuclear Overhauser experiment.[24] The olefinic proton at C(2) in **2** appears as a slightly broadened singlet at 5.66 ppm. Irradiation of a degassed solution of the ester at the resonance position for the protons at C(4) (2.26 ppm) gave a 24 ± 1% enhancement in the integrated intensity of the signal at 5.66 ppm, while irradiation at the alkoxymethylene position (4.71 ppm) gave no enhancement (−1 ± 3%).

An attempt was made to remove the tetrahydropyranyl group in **2**, in order to carry out fluorination prior to reduction of the ester, but even under mild conditions, the only product isolated was α,β-unsaturated lactone **5**. Once



formed, the lactone was extraordinarily resistant to opening, and we were unable to convert it to a related hydroxy ester. Using an alternative approach, **2** was reduced with lithium aluminum hydride, and the new hydroxyl group was protected as an acetate. Removal of the tetrahydropyranyl moiety at this stage gave three new products, the desired 3-hydroxymethyl acetate **6**, the



isomeric 3-acetoxymethyl alcohol **7**, presumably formed by an intramolecular transesterification, and diol **8**. Although the components were easily separated on silica gel, the reaction required careful attention in order to obtain a maximum yield of **6**. Using 0.01 M pyridinium *p*-toluenesulfonate in ethanol, we were able to obtain a 62% isolated yield of 3-(hydroxymethyl)geranyl acetate (**6**) from a mixture that also yielded **7** (18%), **8** (4%), and starting material (6%). With longer reaction times, **3** was completely consumed, but the yield of **6** did not improve because of an increase in the proportion of **6** which isomerized to **7**. Migration of the acetate group was reversible, and treatment of **7** under the conditions used to remove the THP moiety gave a 30% conversion to **6**.

3-(Fluoromethyl)geraniol (**4**) was obtained by treating acetate **6** with (diethylamino)(dimethylamino)sulfur difluoride,[25] followed by hydrolysis of the resulting acetate with potassium carbonate. An initial attempt with DAST, a harsher fluorinating reagent,[25] failed. Introduction of fluorine was accompanied by the disappearance of the two-proton singlet at 4.16 ppm for the hydroxymethyl protons and the appearance of a new doublet (J = 47 Hz) at 4.91 ppm in the ^{1}H NMR spectrum of **4**. In addition, the ^{19}F NMR spectrum showed a triplet (J = 47 Hz) at 212.9 ppm further split by long-range coupling to the protons at C(1) and C(2) (J = 3.3 and 2.8 Hz, respectively). The IR spectrum of our material is similar to that reported by Machleidt[26] for **4**. The overall yield for the six-step synthesis was 18%.

It is also possible to prepare 3-(fluoromethyl)geraniol (**4**) by a sequence which transposes the addition of the organocopper reagent and the fluorination as shown in Scheme II. This route has the advantage of circumventing the problems we encountered with migration of the acetate group upon treatment of **3** with PPTS. However, the conjugate addition of (4-methylpent-3-en-1-yl)copper to **9** proved to be erratic in our hands, with yields ranging from 15% to 50%, and overall, we prefer the former route. Although we did not reduce **10** to **4**, the reaction has been reported by Machleidt[26] to proceed in moderate yield.

3-(Difluoromethyl)geraniol (14). Initially we envisioned two different routes to 3-(difluoromethyl)geraniol (**14**) based on the general sequences shown in Schemes I and II. In each case, the hydroxymethyl moiety was to be oxidized to the corresponding aldehyde, which would then be converted to a difluoromethyl group.[25] When several attempts to oxidize ethyl 4-hydroxy-2-butynoate, including use of manganese dioxide, chromium trioxide in pyridine, and pyridinium chlorochromate, failed, we decided to postpone the fluorination until after construction of the

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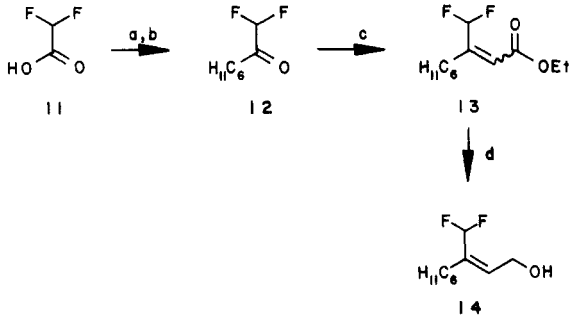
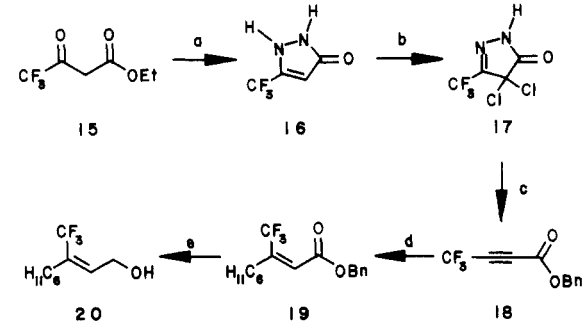
Scheme III.[a] Synthesis of 3-(Difluoromethyl)geraniol



[a] (a) LiOH; (b) $C_6H_{11}MgBr$; (c) $(Et_2O)_2P(O)CH_2CO_2Et$/NaH; (d) $LiAlH_4$, −65 °C.

Scheme IV.[a] Synthesis of 3-(Trifluoromethyl)geraniol

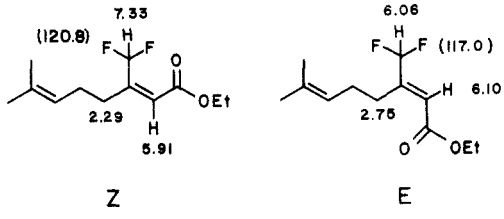


[a] (a) N_2H_2; (b) Cl_2; (c) $AgNO_3$, BnOH; (d) $(C_6H_{11})_2CuLi$, −70 °C; (e) $LiAlH_4$, −20 °C.

geranyl skeleton. Oxidation of ethyl 3-(hydroxymethyl)-geranoate with manganese dioxide gave the corresponding aldehyde in excellent yield. However, several attempts at fluorination with DAST or (diethylamino)(dimethylamino)sulfur difluoride were unsuccessful. Depending on the severity of the reaction conditions, the starting material polymerized or was recovered.

At this point, we resorted to the synthesis shown in Scheme III. Treatment of the lithium salt of difluoroacetic acid (**11**) with (4-methylpent-3-en-1-yl)magnesium bromide afforded difluoromethyl ketone **12** in modest (35%) yield. The subsequent Wittig condensation with triethyl phosphonoacetate gave a 72:28 mixture of geranate and nerate analogues which were separated on silica gel to afford 38% of the desired *Z* isomer, 15% of the *E* isomer, and 7% of a 47:53 *Z*/*E* mixture. Although the separation was not clean, we found that the stereoisomeric alcohols obtained after reduction of (*E*)- and (*Z*)-**13** with lithium aluminum hydride have almost identical mobilities on silica gel and that chromatography must be carried out with the esters. The overall yield of **14** based on difluoroacetic acid was 9% for the five-step sequence.

The stereochemistry of the new C(2)–C(3) double bond was deduced from chemical shifts as described for the fluoromethyl analogue. As expected, on the basis of the known shielding effects of carbethoxy[23] and fluorine[14] substituents, the protons at C(2) and C(4) in the *Z* ester



appear upfield from those in the *E* isomer, while the difluoromethyl proton appears downfield. The fluorines cis to the carboethoxy moiety in ethyl 3-(difluoromethyl)-geranate are shielded by over 3 ppm (chemical shifts in parentheses) relative to the trans-oriented fluorines in the nerate isomer. This behavior is opposite that reported by Camps and co-workers[13] for trifluoromethyl groups in identical orientations.

3-(Trifluoromethyl)geraniol (20). A stereoselective synthesis of 3-(trifluoromethyl)geraniol (**20**) is presented in Scheme IV. On the basis of the difficulties we experienced with the difluoroanalogue, we decided to introduce the trifluoromethyl moiety before the conjugate addition of the 4-methylpent-3-en-1-yl unit in a manner that did not require an oxidation–fluorination sequence. (Trifluoromethyl)acetylenic ester **18** was synthesized from ethyl (trifluoromethyl)acetoacetate (**15**) via pyrazolones **16** and **17** in an overall yield of 55%. The sequence is similar to that reported by Carpino[27] for nonfluorinated acetylenic esters except we found that silver ion was necessary to facilitate the elimination of chloride when the pyrazolone ring has a trifluoromethyl substituent. Benzyl alcohol was selected for the esterification because the resulting ester is not volatile, and benzyl alcohol is easily separated from (trifluoromethyl)geraniol (**20**) by medium-pressure LC after reduction of ester **19** by lithium aluminum hydride. The overall yield for the five-step sequence was 20%.

A single product, assigned as the *Z* stereoisomer **19**, was isolated when the cuprate addition was carried out at −70 °C. The chemical shift of the olefinic proton at C(2) in **19** is 6.02 ppm as compared with values of 5.90 and 6.20 ppm for the C(2) proton of methyl (*Z*)- and (*E*)-3-(trifluoromethyl)farnesates, respectively, reported by Camps and co-workers.[13] Also, when the vinyl copper intermediate in the conversion of **18** to **19** was allowed to warm above −50 °C prior to the quench step, a second, minor product was formed which had a peak at 6.3 ppm, characteristic of the proton at C(2) in the isomeric nerate analogue. Thus, we conclude that the addition of the alkylcopper reagent to acetylene **18** is stereospecific. We had also worried about the possibility that the trifluoromethyl moiety might alter the regiochemistry of the reaction. However, addition of the hydrocarbon moiety to the β-carbon of the unsaturated ester is still the preferred reaction.

Experimental Section

General Methods. Melting points were obtained on a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected as reported. Carbon and hydrogen analyses were determined by Chemalytics, Inc. NMR spectra were recorded on Varian EM-360, EM-390, FT-80, and XL-100 spectrometers. Proton spectra are reported in parts per million downfield from internal tetramethylsilane and fluorine spectra in parts per million upfield from internal trichlorofluoromethane. NMR spectra were obtained in deuteriochloroform (Norell Chemical Co.) or carbon tetrachloride (Mallinkrodt, SpectrAR grade). Infrared spectra were taken on a Beckman Acculab 3 or a Perkin-Elmer 299 infrared spectrophotometer and were calibrated to the 1602-cm^{-1} absorption of polystyrene. Samples were analyzed as 10% solutions in a 0.1-mm path length solution cell vs. a matched reference cell filled with solvent. All absorptions were reported in wave numbers (cm^{-1}). Mass spectra (chemical ionization and electron impact) were obtained on a Varian MAT 112 S mass spectrometer. High-resolution mass spectra were measured on a Varian MAT 731 mass spectrometer and are reported to four decimal places.

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Analytical gas–liquid chromatography was performed on a Varian Aerograph Model 1200 instrument equipped with a Hewlett-Packard Model 3370 B digital integrator. Separation was achieved by using a 500 ft × 0.03 in. i.d., stainless-steel capillary column coated with either Carbowax 20M or SF-96-50 and operated at flow rates of 20 mL/min for nitrogen, 20 mL/min for hydrogen, and 4 mL/min for oxygen. Medium-pressure LC was performed on either a 2.5 cm × 1 m or a 1.25 cm × 1 m column equipped with a 1.8 cm × 21 cm scrubber column. The columns were packed with 40–63-μm silica gel 60 (VWR Scientific), and the solvents were pumped through the columns with a Milton Roy pump. Fractions were collected with a Gilson fractionator. Reactions were routinely monitored by TLC with 7.5 cm × 2.5 cm Baker-flex silica gel 1B-F sheets (J. T. Baker) or silica gel 60 F-254 plates (VWR Scientific). The Baker-flex plates were either visualized with iodine or by dipping in a 10% solution of phosphomolybdic acid in ethanol followed by heating until the spots appeared.

(4-Methylpent-3-en-1-yl)lithium (21). To a stirred suspension of 3.17 g (0.46 mol) of lithium wire (PCR, containing 1% sodium and cut into 3-mm sections) in 30 mL of dry ether were added a few drops of 1,2-dibromoethane. When evolution of ethylene was noticed, 0.556 g (3.4 mmol) of 1-bromo-4-methylpent-3-ene[28] was added dropwise. The flask was then placed in a dry ice/carbon tetrachloride bath (−20 °C), and the remaining portion of the bromide (26.76 g, 0.164 mol) was added as a 1 M solution in dry ether over a 2-h period during which the pot temperature never rose above −5 °C. Stirring was continued for 1 h at −20 °C and for 2 h at 0 °C (ice bath). Filtration with a Schlenk apparatus yielded 123 mL of 0.73 M (4-methylpent-3-en-1-yl)lithium (54%) as determined by titration with dry *sec*-butyl alcohol in benzene with 1,10-phenanthroline as an indicator. The solution was stored at −4 °C prior to use.

Ethyl (*Z*)-3-[[(1′-Oxacyclohex-2′-yl)oxy]methyl]-7-methylocta-2,6-dienoate (2). Procedure A. Prior to the reaction, cuprous iodide (PCR) was washed with dry THF in a Soxhlet extractor and dried overnight at 80 °C under vacuum. A stirred suspension of 2.23 g (11.7 mmol) of cuprous iodide in 50 mL of dry THF was cooled to −60 °C before addition of 16.0 mL of a 0.73 M (11.7 mmol) solution of (4-methylpent-3-en-1-yl)lithium in ether. The mixture was allowed to warm to −32 °C for 1 h and then was cooled to −77 °C before 2.46 g (11.6 mmol) of ethyl 4-[(1-oxacyclohex-2-yl)oxy]but-2-ynoate[29] was slowly added by syringe. The needle was positioned against the side of the flask so the acetylenic ester would cool to the bath temperature before reaching the organocopper reagent. After the mixture was stirred for 2 h at −77 °C, 3 mL of saturated ammonium sulfate solution was added. Stirring was continued at −77 °C for an additional hour before the solution was gradually allowed to warm to room temperature overnight. The organic layer was decanted from the gray precipitate, and the residue was washed with ether. The combined organic fractions were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure to yield 3.25 g of crude material. Purification by medium-pressure LC gave 2.03 g (50%) of a colorless oil: IR (CCl_4) 2930, 2860, 1715, 1640, 1465, 1455, 1380, 1360, 1330, 1265, 1215, 1190, 1165, 1145, 1130, 1090, 1075, 1060, 1040, 985, 920, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3, t, J = 7.2 Hz, CH_3 of ethyl group), 1.48–1.85 (6, m, H at C(3′), C(4′), and C(5′)), 1.61 (3, s, CH_3 at C(7)), 1.68 (3, s, CH_3 at C(7)), 2.26 (4, m, H at C(4) and C(5)), 3.50–3.92 (2, m, H at C(6′)), 4.11 (2, q, J = 7.2 Hz, CH_2 of ethyl group), 4.60 (1, br s, H at C(2′)), 4.71 (2, s, CH_2 at C(3)), 5.09 (1, br t, J = 6 Hz, H at C(6)), 5.66 (1, br t, J = 1.3 Hz, H at C(2)); mass spectrum (CI, isobutane), m/z (relative intensity) 85 (100), 167 (70), 195 (100), 213 (100), 297 (48).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.63; H, 9.14.

Procedure B. The reaction was repeated using 2.55 g (13.4 mmol) of cuprous iodide, 33 mL (24 mmol) of lithium reagent, and 2.48 g (11.7 mmol) of acetylenic ester. Purification by medium-pressure LC afforded 2.42 g (70%) of the desired *Z* isomer, 0.05 g (1%) of an unresolved mixture of *E* and *Z* isomers and 0.137 g (4%) of pure *E* ester, obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.27 (3, t, J = 7.2 Hz, CH_3 of ethyl group), 1.48–1.85 (6, m, H at C(3′), C(4′), and C(5′)), 1.61 (3, s, CH_3 at C(7)), 1.68 (3, s, CH_3 at C(7)), 2.10–2.32 (2, m, H at C(5)), 2.40–2.68 (2, m, H at C(4)), 3.40–3.90 (2, m, H at C(6′)), 4.11 (2, q, J = 7.2 Hz, CH_2 of ethyl group), 4.20 (2, s, CH_2 at C(3)), 4.60 (1, br s, H at C(2′)), 5.09 (1, m, H at C(6)), 5.97 (1, br s, H at C(2)).

4-(4′-Methylpent-3′-en-1′-yl)-1-oxacyclopent-3-en-2-one (5). A solution of 101 mg (0.34 mmol) of ester **2** and 13.8 mg (0.055 mmol) of PPTS in 5 mL of ethanol was heated at 60 °C. The reaction was frequently checked by TLC, and only a single product was formed (R_f 0.57; 1:1 ethyl acetate/hexane). After the starting material (R_f 0.87; 1:1 ethyl acetate/hexane) was consumed, the reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to yield 58 mg (64%) of a colorless oil: IR (CCl_4) 2965, 2920, 1780, 1750, 1640, 1170, 1135, 1055, 920, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (3, s, methyl), 1.69 (3, s, methyl), 2.38 (4, m, H at C(1′) and C(2′)), 4.72 (2, br s, H at C(5)), 5.07 (1, m, H at C(3′)), 5.80 (1, br s, H at C(3)).

(*Z*)-3-[[(1′-Oxacyclohex-2′-yl)oxy]methyl]-7-methylocta-2,6-dien-1-ol (22). A slurry of 0.640 g (17 mmol) of lithium aluminum hydride in 75 mL of dry ether was cooled to −77 °C before addition of a solution containing 4.21 g (8.13 mmol) of ethyl (*Z*)-3-[[(1′-oxacyclohex-2′-yl)oxy]methyl]-7-methylocta-2,6-dienoate in 10 mL of dry ether that was cooled to −77 °C by using a jacketed addition funnel. The ester was added over a 3-min period during which the pot temperature rose to −60 °C. The reaction mixture was allowed to stir for an additional 15 min at −45 °C before addition of 7 mL of saturated sodium chloride solution. After the mixture warmed to room temperature, the organic layer was decanted from the precipitate and the residue washed with ether. The combined ether layers were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure to yield 1.94 g (94%) of a colorless oil. A small sample was purified for analysis by medium-pressure LC: IR (CCl_4) 3620, 3580–3220, 2940, 2870, 1455, 1445, 1380, 1205, 1135, 1120, 1080, 1055, 1020, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–1.76 (6, m, H at C(3′), C(4′), and C(5′)), 1.61 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 2.12 (4, m, H at C(4) and C(5)), 2.61 (1, br s, hydroxyl H), 3.44–3.92 (2, m, H at C(6′)), 4.08 (1, d, J = 11.9 Hz, H_a of CH_2 at C(3)), 4.13 (2, d, J = 6.6 Hz, H at C(1)), 4.17 (1, d, J = 11.9 Hz, H_b of CH_2 at C(3)), 4.62 (1, br s, H at C(2′)), 5.08 (1, br s, H at C(6)), 5.67 (1, t, J = 6.6 Hz, H at C(2)); mass spectrum, m/z (relative intensity) 39.1 (12), 41.1 (83), 43.1 (40), 55.0 (11), 57.0 (12), 67.0 (15), 69.0 (15), 85.1 (100), 254.2 (0.17, M^+).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.69; H, 10.18.

(*Z*)-3-[[(1′-Oxacyclohex-2′-yl)oxy]methyl]-7-methylocta-2,6-dien-1-yl Acetate (3). A solution of 1.84 g (7.25 mmol) of (*Z*)-3-[[(1′-oxacyclohex-2′-yl)oxy]methyl]-7-methylocta-2,6-dien-1-ol, 1.47 mL (15.6 mmol) of acetic anhydride, and 2.3 mL of dry pyridine was allowed to stand at 0 °C for 30 min and for an additional 20 h at room temperature. The mixture was then diluted with 80 mL of ether, washed with water, and dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure yielded 2.07 g (96%) of a colorless oil. A small sample was purified for analysis by medium-pressure LC: IR (CCl_4) 2945, 2870, 2850, 1740, 1465, 1455, 1375, 1370, 1355, 1325, 1230, 1205, 1185, 1155, 1120, 1080, 1055, 1025, 975, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–1.79 (6, m, H at C(3′), C(4′), and C(5′)), 1.59 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 2.03 (3, s, acetate methyl), 2.12 (4, m, H at C(4) and C(5)), 3.42–3.90 (2, m, H at C(6′)), 4.02 (1, d, J = 11.7 Hz, H_a of CH_2 at C(3)), 4.23 (1, d, J = 11.7 Hz, H_b of CH_2 at C(3)), 4.58 (1, br s, H at C(2′)), 4.67 (2, d, J = 6.8 Hz, H at C(1)), 5.08 (1, br s, H at C(6)), 5.49 (1, t, J = 6.8 Hz, H at C(2)); mass spectrum, m/z (relative intensity) 41.1 (39), 43.1 (52), 55.0 (10), 56.9 (13), 67.0 (17), 69.0 (22), 85.1 (100).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.96; H, 9.61.

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(Z)-3-(Hydroxymethyl)-7-methylocta-2,6-dien-1-yl Acetate (6). A solution of 1.25 g (4.2 mmol) of (Z)-3-[[(1'-oxacyclohex-2'-yl)oxy]methyl]-7-methylocta-2,6-dien-1-yl acetate and 0.118 g (0.47 mmol) of PPTS in 50 mL of ethanol was heated at 55 °C for 4 h. After the mixture had cooled to room temperature, the solvent was removed at reduced pressure, and the residue was purified by medium-pressure LC (1:3 ethyl acetate/hexane). The first 160 mL of eluant yielded 72 mg (6%) of starting material, TLC (R_f 0.50; 1:3 ethyl acetate/hexane). The first product eluted between 380 and 700 mL. Removal of solvent yielded 559 mg (62%) of a colorless oil subsequently identified as (Z)-3-(hydroxymethyl)-7-methylocta-2,6-dien-1-yl acetate: TLC (R_f 0.20; 1:3 ethyl acetate/hexane); IR (CCl_4) 3620, 3600–3200, 2975, 2935, 2860, 1740, 1450, 1240, 1025, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 2.02 (3, s, acetate methyl), 2.17 (4, m, H at C(4) and C(5)), 2.63 (1, br s, hydroxyl H), 4.16 (2, s, hydroxymethylene at C(3)), 4.67 (2, d, J = 7.2 Hz, H at C(1)), 5.08 (1, br s, H at C(6)), 5.40 (1, t, J = 7.2 Hz, H at C(2)); mass spectrum, m/z (relative intensity) 41.2 (90), 43.1 (57), 69.1 (100), 83.2 (25).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.62; H, 9.24.

The second product was eluted between 700 and 1170 mL, and removal of solvent yielded 164 mg (18%) of a colorless oil later identified as (Z)-3-(acetoxymethyl)-7-methylocta-2,6-dien-1-ol (7): TLC (R_f 0.15; 1:3 ethyl acetate/hexane); ^1H NMR ($CDCl_3$) δ 1.60 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 2.03 (3, s, acetate methyl), 2.10 (4, m, H at C(4) and C(5)), 3.65 (1, br s, hydroxyl H), 4.18 (2, d, J = 6.9 Hz, H at C(1)), 4.62 (2, s, acetoxymethylene at C(3)), 5.07 (1, br s, H at C(6)), 5.62 (1, t, J = 6.9 Hz, H at C(1)). Treatment of transposed acetate 7 under the above conditions for 7 h afforded a 30% conversion to the acetate 6.

Backwashing the column with ethyl acetate yielded 30 mg (4%) of a pale yellow oil later identified as (Z)-3-(hydroxymethyl)-7-methylocta-2,6-dien-1-ol (8): TLC (R_f 0.04; 1:3 ethyl acetate/hexane); ^1H NMR ($CDCl_3$) δ 1.62 (3, s, CH_3 at C(7)), 1.69, (3, s, CH_3 at C(7)), 2.05 (4, m, H at C(4) and C(5)), 2.68 (2, br s, hydroxyl H), 3.88 (2, s, hydroxymethylene at C(3)), 4.04 (2, d, J = 7 Hz, H at C(1)), 5.02 (1, br s, H at C(6)), 5.56 (1, t, J = 7 Hz, H at C(2)).

(Z)-3-(Fluoromethyl)-7-methylocta-2,6-dien-1-yl Acetate (23). A solution of 223 mg (1.90 mmol) of (dimethylamino)trimethylsilane in 6 mL of trichlorofluoromethane was cooled to −65 °C before addition of 0.29 mL (2.3 mmol) of DAST. The resulting mixture was allowed to stir at −65 °C for 10 min, allowed to warm to room temperature, and cooled to −70 °C prior to addition of 237 mg (1.12 mmol) of (Z)-3-(hydroxymethyl)-7-methylocta-2,6-dien-1-yl acetate. After 45 min, the mixture was allowed to warm to room temperature, and stirring was continued for 1 h before 100 mL of ether and 10 mL of water were added. The organic layer was separated and the aqueous phase extracted with ether. The combined organic layers were then washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to yield 228 mg of crude material. Purification by medium-pressure LC (1.3 cm × 1 m; 1:50 ethyl acetate/hexane) afforded 132 mg (55%) of a colorless oil which was eluted between 530 and 800 mL: TLC (R_f 0.15; 1:50 ethyl acetate/hexane); IR (CCl_4) 2956, 2925, 2860, 1745, 1450, 1375, 1365, 1230, 1025, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 2.02 (3, s, acetate methyl), 2.17 (4, m, H at C(4) and C(5)), 4.62 (2, d d, J = 6.7 Hz, J = 2.7 Hz, H at C(1)), 4.93 (2, d, J = 46.8 Hz, fluoromethyl group at C(3)), 5.07 (1, br s, H at C(6)), 5.52 (1, d t, J = 2.4 Hz, J = 6.7 Hz, H at C(2)); ^{19}F NMR ($CDCl_3$) ϕ 214.5 (q t, J = 2.6 Hz, J = 46.9 Hz); mass spectrum, m/z (relative intensity) 39.1 (17), 41.1 (100), 43.0 (84), 68.0 (13), 69.0 (74).

Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94. Found: C, 67.42; H, 8.81.

(Z)-3-(Fluoromethyl)-7-methylocta-2,6-dien-1-ol (4). A solution of 125 mg (0.59 mmol) of (Z)-3-(fluoromethyl)-7-methylocta-2,6-dien-1-yl acetate in 15 mL of methanol was stirred with 179 mg (1.30 mmol) of potassium carbonate for 10 min at room temperature before addition of 60 mL of ether and 20 mL of saturated ammonium chloride solution. The organic phase was separated and the aqueous layer extracted with ether. The combined ether fractions were washed with water and saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to yield 84 mg (83%) of a colorless oil: IR[26] (CCl_4) 3615, 3560–3110, 2970, 2930, 2920, 2860, 1740, 1710, 1670, 1450, 1380, 1330, 1235, 1180, 1150, 1085, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (1, br s, hydroxyl H), 1.60 (3, s, CH_3 at C(7)), 1.68 (3, s, CH_3 at C(7)), 2.13 (4, m, H at C(4) and C(5)), 4.19 (2, dd, J = 6.7 Hz, J = 3.3 Hz, H at C(1)), 4.91 (2, d, J = 47 Hz, fluoromethyl group at C(3)), 5.07 (1, br s, H at C(6)), 5.65 (1, dt, J = 2.8 Hz, J = 6.7 Hz, H at C(2)); ^{19}F NMR ($CDCl_3$) ϕ 212.9 (tq, J = 47 Hz, J = 2.9 Hz).

Ethyl 4-Fluorobut-2-ynoate (9). A solution containing 5.20 g (32.3 mmol) of DAST in 10 mL of methylene chloride was cooled to −78 °C before addition of 4.88 g (38.1 mmol) of ethyl 4-hydroxy-2-butynoate[29] in 5 mL of methylene chloride. The resulting mixture was allowed to stir for 45 min at −78 °C and 200 min at room temperature before addition of 10 mL of water. The layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic fractions were then washed with water and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure, and the residue was flash distilled to yield 2.49 g (59%) of a colorless oil: bp 28.5–29.0 °C (0.86 mmHg); IR (CCl_4) 2990, 2950, 2910, 2880, 1725, 1480, 1470, 1455, 1380, 1265, 1090, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3, t, J = 7.1 Hz, CH_3 of ethyl group), 4.25 (2, q, J = 7.1 Hz, CH_2 of ethyl group), 5.08 (2, d, J = 46.9 Hz, H at C(4)); ^{19}F NMR ($CDCl_3$) ϕ 226.6 (t, J = 47.1 Hz); mass spectrum, m/z (relative intensity) 27 (16), 29 (18), 45 (20), 57 (32), 66 (25), 85 (100), 129 (0.4), 130 (0.1), 131 (0.2).

Anal. Calcd for $C_6H_7FO_2$: C, 55.38; H, 5.42. Found: C, 55.17; H, 5.17.

Ethyl (Z)-3-(Fluoromethyl)-7-methylocta-2,6-dienoate (10). Following a procedure similar to that described for 2, (4-methylpent-3-en-1-yl)copper was generated from 293 mg (1.54 mmol) of cuprous iodide and 2.5 mL of 0.70 M (4-methylpent-3-en-1-yl)lithium (1.8 mmol). The resulting dark solution was cooled to −90 °C before addition of 207 mg (1.59 mmol) of ethyl 4-fluorobut-2-ynoate (9) over a 5-min period. The resulting mixture was allowed to stir for 2 h at −90 °C before addition of 1.5 mL of saturated ammonium sulfate solution. Workup and chromatography yielded 178 mg (50%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 1.27 (3, t, J = 7 Hz, CH_3 of ethyl group), 1.60 (3, s, CH_3 at C(7)), 1.67 (3, s, CH_3 at C(7)), 1.82–2.38 (4, m, H at C(4) and C(5)), 4.12 (2, q, J = 7 Hz, CH_2 of ethyl group), 5.09 (1, m, H at C(6)), 5.50 (2, d, J = 48.6 Hz, fluoromethyl group at C(3)), 5.68 (1, m, H at C(2)); IR[20] (CCl_4) 2960, 2910, 2840, 1710, 1640, 1445, 1385, 1220, 1160, 1145, 1030 cm^{-1}; ^{19}F NMR ($CDCl_3$) ϕ 230.1 (t, J = 48.9 Hz).

1,1-Difluoro-6-methylhept-5-en-2-one (12). To 1.25 g (13.0 mmol) of difluoroacetic acid (11) was slowly added 3.83 mL of 3.4 M lithium hydroxide (13.0 mmol). Water was removed at reduced pressure, and the resulting residue was dried under vacuum. A 516-mg sample of the lithium salt (5.1 mmol) was suspended in dry ether and cooled to 0 °C before addition of 2.8 mL of a 1.5 M solution of (4-methylpent-3-en-1-yl)magnesium bromide in ether. The resulting suspension was allowed to stir for 30 h at room temperature before it was cooled to 0 °C. The reaction was quenched by addition of 10 g of ice and 1 mL of concentrated hydrochloric acid. The organic layer was separated, and the aqueous layer washed with pentane. The combined organic fractions were washed with sodium bicarbonate and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to yield 774 mg of a residue which gave 240 mg (35%) of a colorless oil upon purification by medium-pressure LC: IR (CCl_4) 2975, 2930, 2920, 1745, 1445, 1405, 1375, 1340, 1105, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (3, s, CH_3 at C(6)), 1.66 (3, s, CH_3 at C(6)), 2.24 (2, q, J = 6 Hz, H at C(4)), 2.62 (2, t, J = 6 Hz, H at C(3)), 4.95 (1, t, J = 6 Hz, H at C(5)), 5.53 (1, t, J = 53 Hz, H at C(1)); ^{19}F NMR ($CDCl_3$) ϕ 126.4 (d, 53.9 Hz); mass spectrum, m/z (relative intensity) 162.1 (12), 111.1 (25), 69.0 (72), 55.0 (33), 43.1 (21), 41.1 (100), 39.1 (21); high-resolution mass spectrum, m/z 161.0777 ($M^+ - 1$, calcd 161.0778), 162.0857 (M^+, calcd 162.0856).

Ethyl (Z)-3-(Difluoromethyl)-7-methylocta-2,6-dienoate (13). A solution of 1.54 g (6.87 mmol) of triethyl phosphonoacetate in 10 mL of benzene was added to a stirred suspension of 301 mg (6.27 mmol) of sodium hydride in benzene at 10 °C. The resulting mixture was allowed to warm to room temperature, and stirring

was continued for 1 h before addition of 988 mg (6.09 mmol) of 1,1-difluoro-6-methylhept-5-en-2-one (12) in 5 mL of benzene. After 3 h at room temperature, the reaction was quenched with 5 mL of 0.4 N hydrochloric acid. The layers were separated, and the aqueous phase was extracted with ether. The combined organic fractions were washed with successive portions of saturated sodium bicarbonate and saturated sodium chloride solutions and then dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure, and the residue was purified by medium-pressure LC (2.5 cm × 1 m; 1.5:98.5 ethyl acetate/hexane). A colorless oil, subsequently identified as ethyl (*Z*)-3-(difluoromethyl)-7-methylocta-2,6-dienoate (13), was eluted between 978 and 1089 mL: 544 mg (38%); TLC (R_f 0.25; 1.5:98.5 ethyl acetate/hexane); IR (CCl_4) 2980, 2930, 2920, 2880, 2870, 1725, 1665, 1445, 1425, 1400, 1385, 1315, 1270, 1250, 1165, 1150, 1100, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3, t, J = 7 Hz, CH_3 of ethyl group), 1.62 (3, s, CH_3 at C(7)), 1.69 (3, s, CH_3 at C(7)), 2.29 (4, br s, H at C(4) and C(5)), 4.17 (2, q, J = 7 Hz, CH_2 of ethyl group), 5.07 (1, br s, H at C(6)), 5.91 (1, br s, H at C(2)), 7.33 (1, t, J = 55.2 Hz, difluoromethyl group at C(3)); ^{19}F NMR ($CDCl_3$) ϕ 120.8 (br d, J = 55.2 Hz); mass spectrum, m/z (relative intensity) 69.0 (100), 116.1 (14), 139.1 (12), 159.2 (13), 164.1 (28), 187.1 (7), 192.1 (11), 212.2 (61), 232.1 (2).

Anal. Calcd for $C_{12}H_{18}F_2O_2$: C, 62.05; H, 7.81. Found: C, 62.30; H, 7.62.

The fractions between 1089 and 1140 mL contained 106 mg (7%) of a 45:55 mixture of *Z*/*E* isomers, and those between 1140 and 1250 mL contained 213 mg (15%) of a colorless oil identified as ethyl (*E*)-3-(difluoromethyl)-7-methylocta-2,6-dienoate ((*E*)-13): TLC (R_f 0.21; 1.5:98.5 ethyl acetate/hexane); IR (CCl_4) 2980, 2930, 2920, 2880, 2870, 1725, 1665, 1450, 1385, 1365, 1350, 1325, 1300, 1245, 1215, 1170, 1150, 1110, 1080, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3, t, J = 7.2 Hz, CH_3 of ethyl group), 1.63 (3, s, CH_3 at C(7)), 1.70 (3, s, CH_3 at C(7)), 2.13–2.42 (2, m, H at C(5)), 2.67–2.84 (2, m, H at C(4)), 4.24 (2, q, J = 7.2 Hz, CH_2 at ethyl group), 5.18 (1, br t, J = 7 Hz, H at C(6)), 6.06 (1, t, J = 56 Hz, difluoromethyl group at C(3)), 6.10 (1, br s, H at C(2)); ^{19}F NMR ($CDCl_3$) ϕ 117.0 (d, J = 56 Hz).

Anal. Calcd for $C_{12}H_{18}F_2O_2$: C, 62.05; H, 7.81. Found: C, 61.96; H, 7.80.

(*Z*)-3-(Difluoromethyl)-7-methylocta-2,6-dien-1-ol (14). To a stirred slurry of 41 mg (1.1 mmol) of lithium aluminum hydride in 30 mL of dry ether at −65 °C was added 262 mg (1.1 mmol) of ethyl (*Z*)-3-(difluoromethyl)-7-methylocta-2,6-dienoate in 20 mL of dry ether cooled to −65 °C in a jacketed addition funnel. The resulting mixture was allowed to stir for 45 min at −60 °C and then quenched with 0.4 mL of saturated sodium chloride solution. After the pot had warmed to room temperature, an additional 0.7 mL of saturated sodium chloride was added, and the organic layer was decanted from the precipitate.

The residue was washed with ether, and the combined ether fractions were dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure and the residue purified by medium-pressure LC, affording 148 mg (69%) of a colorless oil: IR (CCl_4) 3610, 3500–3200, 2965, 2915, 2860, 1450, 1400, 1365, 1100, 1015, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3, s, CH_3 at C(7)), 1.68 (3, s, CH_3 at C(7)), 1.72 (1, s, hydroxyl H), 2.13 (4, m, H at C(4) and C(5)), 4.24 (2, dt, J = 6.6 Hz, J = 2.7 Hz, H at C(1)), 5.07 (1, br s, H at C(6)), 5.72 (1, t, J = 6.6 Hz, H at C(2)), 6.42 (1, t, J = 56 Hz, difluoromethyl group at C(3)); ^{19}F NMR ($CDCl_3$) ϕ 116.2 (d, J = 56 Hz); mass spectrum, m/z (relative intensity) 53.1 (8), 58.9 (7), 67.0 (6), 68.0 (5), 69.1 (100), 70.1 (6).

Anal. Calcd for $C_{10}H_{16}F_2O$: C, 63.13; H, 8.48. Found: C, 63.35; H, 8.46.

5-(Trifluoromethyl)-4-pyrazolin-3-one (16). A solution of hydrazine hydrate (5.0 g of a 64% aqueous solution, 100 mmol) was slowly added to 18.4 g (100 mmol) of ethyl 4,4,4-trifluoroacetoacetate (15) in 150 mL of 95% ethanol. The resulting mixture was heated at reflux for 18 h, and the solvent was removed at reduced pressure to yield 14.9 g (98%) of a pale yellow solid: mp 208–211 °C; IR (KBr) 3280, 1600, 1500, 1425, 1260, 1150, 1100, 1005, 790, 710 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.77 (1, s, H at C(4)), 9.80 (2, s, H at nitrogen); ^{19}F NMR (acetone-d_6) ϕ 61.4 (s); mass spectrum, m/z (relative intensity) 40.1 (8), 43.1 (7), 44.1 (9), 51.0 (7), 53.0 (19), 55.9 (13), 69.0 (53), 75.0 (90), 76.1 (48), 103.0 (54), 132.0 (54), 133.0 (37), 152.1 (100), 153.1 (19).

Anal. Calcd for $C_4H_3F_3N_2O$: C, 31.58; H, 1.99; N, 18.42. Found: C, 31.31; H, 1.80; N, 18.62.

4,4-Dichloro-5-(trifluoromethyl)-5-pyrazolin-3-one (17). Chlorine was gently bubbled through a stirred slurry of 11.4 g (75 mmol) of 5-(trifluoromethyl)-4-pyrazolin-3-one (16) in 300 mL of dry dichloromethane for 30 min. The solvent was decanted, the residue suspended in an additional 200 mL of dry dichloromethane, and the resulting slurry treated with chlorine as previously described. The solvent was again decanted and removed from the combined fractions under vacuum. Distillation of the residue yielded 11.9 g (72%) of a clear, viscous oil: bp 85–86 °C (4.7 mmHg); IR (neat) 3300, 1775, 1605, 1415, 1220, 1165, 1080, 1010, 875, 775, 720, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.66 (br s); ^{19}F NMR ($CDCl_3$) ϕ 64.0 (s); mass spectrum, m/z (relative intensity) 36.0 (21), 47.0 (13), 69.0 (100), 71.0 (25), 74.0 (25), 82.0 (100), 84.0 (100), 86.0 (20), 87.0 (12), 93.0 (68), 108.0 (10), 109.0 (88), 110.0 (11), 111.0 (30), 121.0 (15), 128.0 (20), 176.9 (28), 178.9 (17), 185.0 (72), 187.0 (22), 191.0 (100), 193.0 (80), 195 (12), 220.0 (51), 222.0 (32), 224.0 (5).

Anal. Calcd for $C_4H_1Cl_2F_3N_2O$: C, 21.54; H, 0.46; N, 12.68. Found: C, 21.58; H, 0.55; N, 12.95.

Benzyl 4,4,4-Trifluorobutynoate (18). A stirred suspension of 8.5 g (50 mmol) of silver nitrate and 5.1 g (50 mmol) of triethylamine in 50 mL of dry dichloromethane was cooled to −78 °C before addition of 4.44 g (20 mmol) of 4,4-dichloro-5-(trifluoromethyl)-5-pyrazolin-3-one (17) in 10 mL of dichloromethane. The resulting slurry was allowed to warm to −25 °C and allowed to stir for 20 min before being recooled to −78 °C. After addition of 13 g (120 mmol) of benzyl alcohol, the reaction mixture was allowed to warm to 0 °C over a 45-min period. Gas evolution was noticed as the pot warmed to −25 °C, and slow warming was necessary to control the rate of the evolution. The reaction was maintained at 0 °C until bubbling ceased (~20 min) and was quenched by addition of 50 mL of ice-cold 5% hydrochloric acid. The resulting mixture was extracted with pentane, and the combined organic fractions were dried over anhydrous magnesium sulfate. Sovent was removed at reduced pressure, and the residue purified by medium-pressure LC to yield 3.56 g (78%) of a clear oil: IR (neat) 3060, 3020, 2950, 1725, 1490, 1450, 1370, 1270, 1150, 990, 950, 900, 740, 690, 650 cm^{-1}; ^1H NMR (CCl_4) δ 5.30 (2, s, CH_2 of benzyl group), 7.48 (5, s, aromatic H); ^{19}F NMR ($CDCl_3$) ϕ 52.8 (s).

Anal. Calcd for $C_{11}H_7F_3O_2$: C, 57.90; H, 3.09. Found: C, 57.64; H, 3.05.

Benzyl 3-(Trifluoromethyl)-7-methylocta-2,6-dienoate (19). By use of a procedure similar to that for 2, (4-methylpent-3-en-1-yl)copper was generated from 1.7 mL of 1.6 M (4-methylpent-3-en-1-yl)lithium (2.7 mmol) and 0.50 g (2.7 mmol) of cuprous iodide in 5 mL of dry THF. The resulting dark solution was cooled to −70 °C before addition of 0.30 g (1.3 mmol) of benzyl 4,4,4-trifluorobutynoate (18). After 20 min, the reaction was quenched and worked up to yield a yellow residue. Purification by medium-pressure LC (R_f 0.30; 1:50 ethyl acetate/hexane) gave 0.22 g (53%) of a colorless oil: IR (neat) 3060, 3040, 2990, 2960, 1740, 1670, 1500, 1450, 1380, 1335, 1260, 1150, 1090, 1030, 750, 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.61 (3, s, CH_3 at C(7)), 1.70 (3, s, CH_3 at C(7)), 2.27 (4, m, H at C(4) and C(5)), 5.15 (1, m, H at C(6)), 5.20 (2, s, CH_2 of benzyl group), 6.02 (1, s, H at C(2)), 7.41 (5, s, aromatic H); ^{19}F ($CDCl_3$) ϕ 64.1 (br s).

Anal. Calcd for $C_{17}H_{19}F_3O_2$: C, 65.37; H, 6.13. Found: C, 65.38; H, 6.05.

7-Methyl-3-(trifluoromethyl)octa-2,6-dien-1-ol (20). Following a procedure similar to that described for 14, 4.5 g (1.44 mmol) of benzyl 3-(trifluoromethyl)-7-methylocta-2,6-dienoate (19) was added to a stirred solution of 110 mg (2.9 mmol) of lithium aluminum hydride in 25 mL of dry ether at −78 °C. The mixture was allowed to warm to −20 °C over a 30-min period and worked up to give a light yellow residue. Purification by medium-pressure LC yielded 208 mg (69%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 1.61 (3, s, CH_3 at C(7)), 1.69 (3, s, CH_3 at C(7)), 2.22 (4, m, H at C(4) and C(5)), 4.37 (2, m, H at C(1)), 5.09 (1, m, H at C(6)), 5.87 (1, br t, J = 6 Hz, H at C(2)); ^{19}F NMR ($CDCl_3$) ϕ 62.5 (t, J = 2.4 Hz).

Anal. Calcd for $C_{10}H_{15}F_3O$: C, 57.68; H, 7.26. Found: C, 57.52; H, 7.37.

Registry No. 1, 31555-03-0; (*E*)-2, 76480-86-9; (*Z*)-2, 76480-87-0; 3, 76480-88-1; 4, 76480-89-2; 5, 61315-75-1; 6, 76480-90-5; 7, 76480-91-6; 8, 76480-92-7; 9, 76480-93-8; 10, 76480-94-9; 11, 381-73-7; 12, 76480-95-0; (*E*)-13, 76480-96-1; (*Z*)-13, 76480-97-2; 14, 76480-98-3; 15, 372-31-6; 16, 76480-99-4; 17, 76481-00-0; 18, 76481-01-1; 19, 76481-02-2; 20, 76481-03-3; 21, 64504-53-6; 22, 76481-04-4; 23, 76481-05-5; 1-bromo-4-methylpent-3-ene, 2270-59-9; ethyl 4-hydroxy-2-butynoate, 31555-04-1; (4-methylpent-3-en-1-yl)copper, 54248-40-7; triethyl phosphonoacetate, 867-13-0.

Synthetic Route to 6-Functionalized 2-Azabicyclo[3.3.1]nonanes[1]

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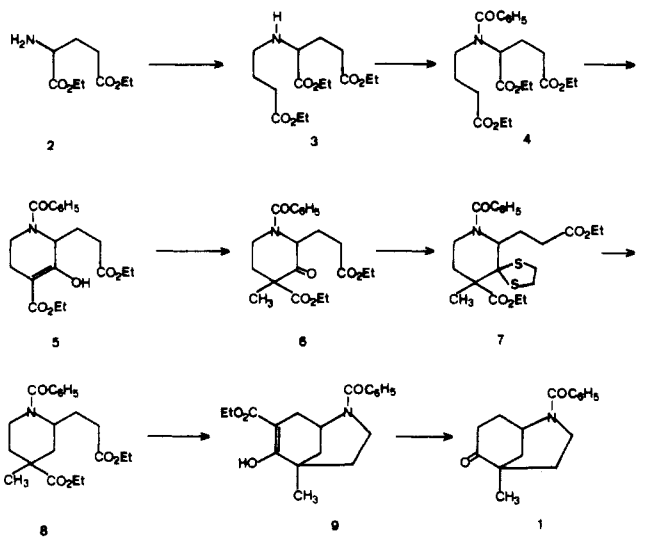
The synthesis of a 5-alkyl-2-azabicyclo[3.3.1]nonan-6-one by Dieckmann cyclization followed by decarbethoxylation from an appropriate piperidine diester, 8, is described. Monoalkylation of diethyl glutamate with ethyl 4-bromobutyrate and further benzoylation gave diethyl *N*-benzoyl-*N*-[3-(ethoxycarbonyl)propyl]glutamate (4). The ring closure of this triester by Dieckmann reaction followed by alkylation of the resulting 4-(ethoxycarbonyl)-3-piperidone 5 led to a diastereomeric mixture of 6 which was converted into the required piperidine diester 8, also in the form of a diastereomeric mixture, via the ethylene dithioketal 7 and subsequent desulfurization.

The 2-azabicyclo[3.3.1]nonane system[2] appears in numerous alkaloids (e.g., morphine, strycnine, uleine) and various synthetic compounds both of analgesic (morphinans, benzomorphans, and 5-phenylmorphans) and structural interest (2-azaadamantane). When functionalized, 2-azabicyclo[3.3.1]nonanes have been used as intermediates in the synthesis of more complex polycyclic structures,[3] especially those related to indole alkaloids[4] and to potentially active systems from a pharmacological standpoint.[5]

Our interest in the field of functionalized 2-azabicyclo[3.3.1]nonanes is focused on the possibilities they offer as intermediates in the synthesis of heteromorphans,[6] as they will allow us to adopt a new approach to such systems which, in general, have been prepared by acid-induced cyclization of 2-(heteroarylmethyl)tetrahydropyridines[7] with the limitations that this implies in some heterocyclic systems.[7e,8] In this context we intended to synthesize a

Scheme I



5-alkyl-2-azabicyclo[3.3.1]nonan-6-one, whose structural characteristics would allow the unequivocal elaboration of heteroaromatic systems fused between the 6- and 7-positions of the morphan nucleus, leading to heteromorphans[9] with a quaternary carbon atom directly attached to the aromatic ring. Such a condition is considered fundamental in synthetic analgesics[10] related to morphine.

The route we propose for the synthesis of 2-benzoyl-5-methyl-2-azabicyclo[3.3.1]nonan-6-one (1, Scheme I) implies the formation of the functionalized carbocyclic ring via Dieckmann cyclization followed by decarbethoxylation from an appropriate piperidine, 8. In turn, the polysubstituted piperidine 8, with the required methyl group for the subsequent localization of a C-5 alkyl substituent on morphan 1, can be prepared from a 4-(ethoxycarbonyl)-3-piperidone such as 5 by alkylation followed by reduction of the ketone carbonyl group. The β-keto ester 5, key intermediate of this synthetic scheme, can be obtained by

(1) This work was presented in a preliminary form at the First European Symposium on Organic Chemistry, Cologne, 1979.

(2) The 2-azabicyclo[3.3.1]nonanes are also frequently named morphans. For a review on the synthesis of such systems see J. Bosch and J. Bonjoch, *Heterocycles*, 14, 505 (1980).

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(6) Heteromorphans are compounds coming from isosteric substitution by an heterocyclic ring of the benzene nucleus in 6,7-benzomorphans in which the heteroaromatic ring is fused between the 6- and 7-positions of the 2-azabicyclo[3.3.1]nonane system.

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