A Short Synthesis of (3Z,6E)-α-Farnesene

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Introduction

The sesquiterpene hydrocarbon α-farnesene has four stereoisomers (**1**–**4**), as well as positional isomers (β-farnesene **5** and allofarnesene **6**). (*E*,*E*)- and (*Z*,*E*)-α-farnesene have been identified from a number of plants, such as apples[1] and pears,[2] chrysanthemums,[3] and the oils of *Perilla*[4] and *Achiiea ptarmica*.[5] α-Farnesenes have also been identified in extracts from a number of insects, including several ant species,[6a–f] a cotton seed bug,[7] and in the pheromone secretions of two fruit fly species of major economic importance, the Caribbean fruit fly[8] and the Mediterranean fruit fly.[9]

Several syntheses of α-farnesene isomers have been published. However, most of the available syntheses generate complex mixtures, from which pure compounds can be separated only with difficulty. For example, nerolidol and farnesol have been dehydrated at elevated temperatures, producing complex mixtures of farnesenes plus degradation products, from which farnesene isomers were isolated in milligram quantities by preparative gas chromatography.[7,10] Rhodium chloride-catalyzed isomerization of trans-β-farnesene similarly furnished a complex mixture.[11] A multistep, low-yielding synthesis starting from farnesol has also been reported.[12] More recently, Morgan et al. prepared a mixture of (*Z*,*E*)- and (*Z*,*Z*)-α-farnesenes using Wittig chemistry; the resulting mixture of isomers (34% yield overall) was separated by HPLC.[6c]

Our objective was to develop a short, straightforward synthesis of (*Z*,*E*)-α-farnesene, in order to provide sufficient quantities for bioassaying as a potential attractant for the Caribbean and Mediterranean fruit flies.

Results and Discussion

The α-farnesene structure appears deceptively simple, and a number of unsuccessful synthetic routes were attempted before settling on the route shown in Scheme 1. These unsuccessful routes included attempted Wittig reaction of the anion of homogeranyl triphenylphosphonium bromide or chloride with methyl vinyl ketone, 1-butyn-3-one, and other potential methyl vinyl ketone equivalents (1-chloro- or 1-tosylbutan-3-one). A variety of different bases (butyllithium, LDA, potassium *tert*-butoxide, NaOEt, DBU, $NaCH_2SOCH_3$, NaH), solvents (THF, ether, DMSO, DME), and temperature regimes were tried, but at best, (*Z*,*E*)-α-farnesene was produced only as a minor component of a complex mixture. Attempts at selective dehydration, bromination/dehydrobromination (Ph_3PBr_2), or iodination/dehydroiodination ($(PhO)_3PMeI$)[13] of (*E*)-nerolidol by several methods were likewise no more successful.

A satisfactory route was finally developed based on the Horner modification of the Wittig reaction.[14] With this method, the carbanion formed is stabilized by the attached diphenylphosphine oxide group. Upon reaction with a ketone or aldehyde, stable and isolable diastereomeric intermediates which can be separated chromatographically are produced. The reaction conditions (solvent, temperature) can be adjusted to give a preponder-

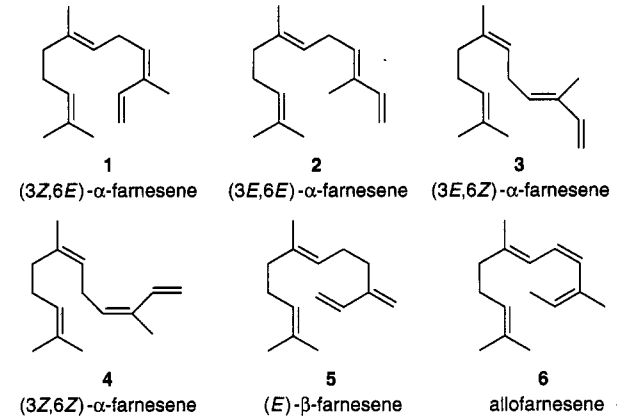
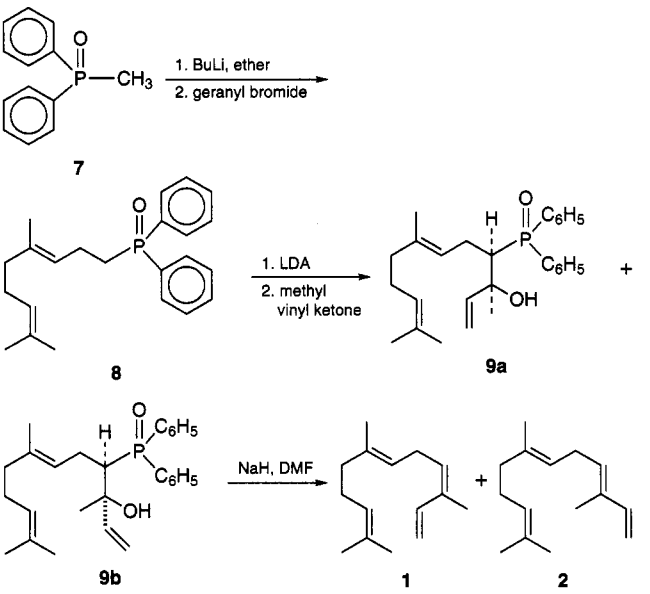


Figure 1.

Scheme 1



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ance of the erythro diastereomer, which, upon treatment with base, undergoes a syn elimination of the water soluble diphenylphosphinic acid, producing the cis alkene.

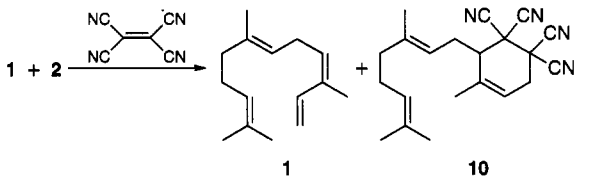
The successful synthesis (Scheme 1) commenced with geranyl bromide, which provided 10 of the 15 carbons on the farnesene skeleton, including the critical 6*E* double bond in the final product. Reaction of geranyl bromide with the carbanion from methyldiphenylphosphine oxide (**7**) gave the one-carbon homolog **8** in reasonable yield after chromatographic purification. Treatment of **8** in ether with *n*-butyllithium at −78 °C followed by the slow addition of methyl vinyl ketone gave the β-hydroxy phosphine oxides **9a** and **9b** in an unsatisfactory 35% yield. Substituting LDA for butyllithium approximately doubled the yield, giving **9a** and **9b** as a mixture of stable diastereomers (**9a**:**9b**, 4:1) in 65% isolated yield. Carrying out the reaction in THF instead of diethyl ether gave no improvement in yield.

Attempts at large-scale separation of **9a** and **9b** by recrystallization were not successful, but the diastereomers were readily separable by normal phase HPLC. The proton NMR spectra of the two diastereomers showed distinctly different signals for the methyl group on C_3 and for the olefinic protons on C_1 and C_2. The stereochemistries of **9a** and **9b** were assigned by determination of which farnesene isomer resulted from the syn-elimination of the elements of diphenylphosphinic acid from **9a** or **9b** in the next step. In any event, it proved easier to carry out the elimination step on the mixture of diastereomers **9a** and **9b**, followed by the selective removal of the unwanted *E,E*-isomer (*vide infra*).

The base-induced elimination of diphenylphosphinic acid from **9a** or **9b** was highly stereoselective, providing moderate yields of (*Z,E*)- or (*E,E*)-α-farnesenes, respectively, with isomeric purities of 98%. However, the reaction proved to be very sensitive to the conditions used, with unwanted isomers and nonvolatile degradation products being produced readily. After lengthy experimentation with different bases (butyllithium, LDA, potassium *tert*-butoxide, KOH, NaOMe, NaOEt, CH_3OK, $NaNH_2$, CsF, NaH), solvents (THF, ether, DMSO, DMPU, CH_3OH, DMF, H_2O), temperatures, and concentrations, the optimal conditions for the elimination were determined to be the rapid addition of NaH to a warmed DMF solution of **9**, quenching the reaction as soon as all the starting material had been consumed (approximately 5 min). Even under these conditions, modest yields of **1** and **2** (41%; *Z,E* to *E,E*, 4:1) were obtained, albeit free of undesired side products. Monitoring the reactions in this and the subsequent step was complicated by the facile rearrangement of the farnesene products at temperatures above about 140 °C, for example, in the GC injection port. Consequently, GC analyses were carried out with an injector temperature and maximum oven temperature of 120 °C.

Knight et al. had previously reported the removal of (*E,E*)-α-farnesene from a mixture of farnesene isomers by selective Diels–Alder reaction of the unwanted *E,E* isomer with maleic anhydride in chloroform.[7] We chose to use the powerful dienophile tetracyanoethylene instead.[15] Thus, reaction of the mixture of farnesenes **1** and **2** with tetracyanoethylene at room temperature in ether resulted in the selective reaction of the less sterically hindered *E,E*-isomer **2**, giving the Diels–Alder adduct **10**. Pure (*E,Z*)-**1** was then readily separated from

Scheme 2



1 **10**

adduct **10** and unreacted tetracyanoethylene by percolation of the worked up mixture through a column of neutral alumina, eluting with pentane. The NMR, IR, and mass spectra of **1** closely matched those previously reported.[7,10]

As previously described,[6c] α-farnesene isomers, even after careful purification, were unstable; neat material exposed to light and air in flasks on the benchtop polymerized in a matter of hours. To minimize degradation, pure **1** and **2** were stored in brown glass vials under nitrogen at −20 °C, as dilute solutions (10%) in pentane, with a few crystals of antioxidant (butylated hydroxytoluene) added as a further precaution.

In summary, a short four-step synthesis of (*Z,E*)-α-farnesene (**1**), which can be scaled up to produce multigram quantities, has been developed. This synthetic route also allows access to (*E,E*)-α-farnesene (**2**), either by separation of the diastereomeric intermediates **9a** and **9b**, or by chromatographic separation of **1** and **2** after the elimination step. Furthermore, the synthesis should be readily adaptable to the syntheses of the (*Z,Z*)- and (*E,Z*)-α-farnesene isomers (**3** and **4**) by substitution of neryl bromide for geranyl bromide as the starting material.

Experimental Procedures

Melting points are not corrected. Proton NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$, on a General Electric QE-300 instrument. IR spectra were obtained as KBr pellets or neat films on NaCl plates, on a Perkin-Elmer 727 IR spectrometer. Electron impact mass spectra (70 eV) were recorded with a Hewlett-Packard 5970B mass selective detector coupled to a HP 5890 gas chromatograph (GC) fitted with a DB5-MS column (20 m x 0.2 mm i.d., J&W Scientific, Folsom, CA). Electron impact mass spectra (20 eV) were recorded with an HP 5989 mass spectrometer interfaced to an HP 5890 GC fitted with a DB-5 column (20 m × 0.25 mm i.d.). FAB mass spectra were taken with a VG-ZAB mass spectrometer, using *m*-nitrobenzyl alcohol as the matrix. Mass spectra are reported as *m/z* (abundance). Routine GC analyses were carried out on a HP 5890 GC fitted with a DB-5 column (20 m × 0.32 mm i.d.). Elemental analyses were performed by Desert Analytical (Tucson, AZ). All synthetic operations were carried out in oven-dried glassware.

Ether and THF were purified by distillation from sodium benzophenone ketyl under nitrogen. Dimethylformamide was distilled from calcium hydride at reduced pressure (20 mmHg) under nitrogen. Unless otherwise specified, worked up reaction mixtures were dried with anhydrous Na_2SO_4 and concentrated by rotary evaporation under reduced pressure. Solvents for flash chromatography (hexane and EtOAc) were distilled prior to use. Flash chromatography[16] was carried out using silica gel grade 60, 230–400 mesh (Aldrich Chemical Co.). Methyl vinyl ketone and geranyl bromide were distilled under reduced pressure immediately prior to use.

1-(Diphenylphosphinyl)-4,8-dimethyl-3,7-nonadiene (8). *n*-Butyllithium (52 mL, 83 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of methyl diphenylphosphine oxide (**7**) (16.50 g, 76 mmol, Lancaster Synthesis, Windham, NH) in dry ether (250 mL) at 0 °C under nitrogen. The solution was

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warmed to 20 °C and stirred for 15 min and then cooled to −78 °C, and a solution of geranyl bromide (16.50 g, 76 mmol; Aldrich Chemical Co.) in dry ether (200 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min, warmed to room temperature, and stirred a further 30 min. The solution was then poured into saturated NH_4Cl solution, and after shaking, the organic layer was removed. The aqueous phase was extracted with ether (2 × 100 mL), and the combined organic extracts were washed with water (2 × 25 mL), dried, and concentrated. The crude product was flash chromatographed in 6 g batches on a 5 × 25 cm column, eluting with 60% EtOAc in hexane, and then Kugelrohr distilled, yielding 19.25 g (72%) of light yellow liquid, bp ~250 °C (oven)/0.05 mmHg. IR (neat) 1440, 1180, 1120 cm^{-1}. ^{1}H-NMR δ 7.70−7.82 (m, 4H), 7.42−7.55 (m, 6H), 5.02−5.16 (m, 2H), 2.23−2.40 (m, 4H), 1.87−2.08 (m, 4H), 1.68 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H). ^{13}C-NMR δ 136.60, 133.20 (d, J_{P-C} = 97.70 Hz), 131.62 (d, J_{P-C} = 2.51), 131.43, 130.81 (d, J_{P-C} = 9.27 Hz), 128.67 (d, J_{P-C} = 12.44 Hz), 124.09, 122.96 (d, J_{P-C} = 15.30 Hz), 39.25, 30.10 (d, J_{P-C} = 70.30 Hz), 26.51, 25.68, 20.06 (d, J_{P-C} = 3.2 Hz), 17.68, 16.00. MS (FAB, *m*-nitrobenzyl alcohol) 353 (MH^+, 100), 297 (3), 285 (8), 263 (3), 229 (5), 215 (17), 201 (Ph_2PO^+), (22), 181 (3), 154 (4), 140 (4), 125 (10). Anal. Calcd for $C_{23}H_{29}OP$: C, 78.38; H, 8.29. Found: C, 78.03; H, 8.23.

(6*E*)-*erythro*- and *threo*-3,7,11-Trimethyl-4-(diphenylphosphinyl)dodecatrien-3-ol (9a and 9b). To a cold (0 °C) solution of homogeranylphosphine oxide **8** (13.2 g, 37 mmol) in ether (300 mL) under nitrogen was added a solution of lithium diisopropylamide (LDA) (37 mL, 55 mmol, 1.5 M) *via* syringe. The resulting yellow solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of methyl vinyl ketone (4.44 g, 63 mmol) in ether (52 mL) was added *via* syringe over 1 h. The solution was stirred at −78 °C for 30 min and then warmed to 25 °C and stirred for 30 min. The reaction mixture was poured into water and extracted three times with ether. The combined ether extracts were washed with water and brine, dried, and concentrated. The residue was flash chromatographed in five batches, eluting with hexane:ethyl acetate (3:2) to give 10.18 g (65%) of diastereoisomers **9a** and **9b** (≈4:1 ratio), mp 86 °C. IR (KBr pellet) 3400, 1440, 1180 cm^{-1}. Anal. Calcd for $C_{27}H_{35}O_2P$: C, 76.77; H, 8.29. Found: C, 76.53; H, 8.35.

The diasteromers **9a** and **9b** were separated by normal phase HPLC, using an HP 1050 pump, an Econosil column (25 × 2.25 cm i.d., 10 μm particle size; Alltech Assoc., Deerfield, IL), and a 3 × 0.9 cm guard column packed with the same material, eluting isocratically with THF:hexane (44:56, flow rate 5 mL/min). The stereochemistries of **9a** and **9b** were assigned by determining which farnesene isomer resulted from the syn-elimination of the elements of diphenylphosphinic acid in the following step. ^{1}H NMR, early eluting erythro diastereomer **9a** (Scheme 1) δ 7.80−7.88 (m, 2H), 7.68−7.78 (m, 2H), 7.37−7.57 (m, 6H), 5.84 (dd, 1H, *J* = 17.10, 10.72 Hz), 5.58 (s, 1H, OH), 5.38 (dd, 1H, *J* = 17.24, 1.52 Hz), 4.98−5.08 (m, 2H), 4.77 (br t, 1H, *J* = 6.5 Hz), 2.55−2.63 (m, 1H), 2.22−2.53 (m, 2H), 1.87−1.98 (m, 2H), 1.73−1.85 (m, 2H), 1.69 (s, 3H), 1.59 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H). ^{13}C-NMR δ 142.70 (d, J_{P-C} = 8.38 Hz), 136.07, 135.20 (d, J_{P-C} = 93.63 Hz), 132.31, 131.74 (d, J_{P-C} = 2.68 Hz), 130.41 (d, J_{P-C} = 8.99 Hz), 128.25 (d, J_{P-C} = 11.72 Hz), 124.12, 123.65 (d, J_{P-C} = 6.71 Hz), 113.40, 76.25 (d, J_{P-C} = 3.40 Hz), 46.82 (d, J_{P-C} = 66.24 Hz), 39.50, 30.09 (d, J_{P-C} = 6.74 Hz), 26.32, 25.71, 24.92, 17.73, 16.02. MS (FAB, *m*-nitrobenzyl alcohol) 423 (MH^+, 34), 405 (35), 391 (2), 351 (10), 337 (4), 314 (2), 269 (24), 255 (5), 229 (7), 201 (100), 185 (6), 155 (7), 125 (8), 109 (7). ^{1}H NMR, late eluting threo diastereomer **9b** (Scheme 1) δ 7.72−7.86 (m, 4H), 7.38−7.53 (m, 6H), 5.70 (dd, 1H, *J* = 17.13, 10.61 Hz), 5.26 (dd, 1H, *J* = 17.76, 0.99 Hz), 5.14 (s, 1H, OH), 5.05 (br t, 2H), 4.93 (m, 2H), 4.69 (dd, 1H, *J* = 10.4, 1.06 Hz), 2.48−2.68 (m, 2H), 2.21−2.40 (m, 1H), 1.91−2.02 (m, 2H), 1.80−1.90 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H). ^{13}C-NMR δ 144.54 (d, J_{P-C} = 5.19 Hz), 136.13, 134.80 (d, J_{P-C} = 94.44), 133.29, 131.40 (d, J_{P-C} = 2.97 Hz), 130.83 (d, J_{P-C} = 8.97 Hz), 128.38 (d, J_{P-C} = 11.55 Hz), 124.13, 123.99 (d, J_{P-C} = 7.15 Hz), 112.59, 76.16 (d, J_{P-C} = 3.48 Hz), 46.80 (d, J_{P-C} = 67.00 Hz), 39.54, 27.00 (d, J_{P-C} = 7.68 Hz), 26.35, 25.71, 24.30, 17.72, 15.96.

(3*Z*,6*E*)- and (3*E*,6*E*)-α-Farnesenes (1 and 2). NaH (0.25 g, 10 mmol) was added in one portion to the mixture of phosphine oxide stereoisomers **9a** and **9b** (5 g, 11 mmol) in dry DMF (100 mL) at 50 °C under dry nitrogen. After 5 min at 50 °C, the reaction mixture was cooled, poured into water, and extracted with ether. The ethereal extract was washed thoroughly with water and then brine, dried (anhyd $MgSO_4$), and concentrated. The residue was Kugelrohr distilled, yielding 0.99 g (41%) of farnesenes **1** and **2**, bp ~100 °C (oven)/0.05 mm, in a 4:1 ratio.

In similar fashion, the isolated stereoisomers **9a** and **9b**, upon reaction with NaH, produced (*Z*,*E*)- and (*E*,*E*)-α-farnesenes **1** and **2** in 45% and 46% yields (98% pure by GC), respectively.

(3*Z*,6*E*)-α-Farnesene (1). Tetracyanoethylene (0.188 g, 1.4 mmol) was added to a mixture of **1** and **2** (0.50 g, 2.4 mmol) in ether (5 mL) under nitrogen at room temperature, and the resulting solution was stirred 30 min. The mixture was concentrated by rotary evaporation, and the residue was washed through a column of neutral alumina, eluting with pentane, giving 0.32 g (64%) of (*Z*,*E*)-α-farnesene (**1**) as a clear liquid, which was Kugelrohr distilled to remove traces of alumina, which might catalyze decomposition (bp ~90 °C (oven)/0.05 mm. ^{1}H-NMR δ 6.89−6.78 (q, 1H, *J* = 11, 16 Hz), 5.4−5.05 (m, 5H), 2.86 (t, 2H, *J* = 7.0 Hz), 2.12−1.95 (m, 4H), 1.81 (s, 3H), 1.7 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H). ^{13}C-NMR δ 135.65, 133.67, 131.91, 131.41, 129.73, 124.24, 122.35, 113.44, 39.66, 26.67, 26.36, 25.69, 19.75, 17.68, 16.10. MS (EI, 20 eV) 204 (1), 189 (2), 161 (7) 147 (3), 135 (4), 123 (8), 107 (32), 119 (100), 93 (97), 79 (29), 69 (56), 55 (44), 41 (32).

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