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γ-ALKYLATION OF α,β-UNSATURATED ACIDS

A TECHNIQUE OF STEREOSPECIFIC ISOPRENOID HOMOLOGATION[a]

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Abstract—This paper describes the synthesis of various isomers of farnesol by means of two different isoprenoid homologations; the γ-alkylation of 2-butynoic acid and the γ-alkylation of 3-methyl crotonic acid.

Recently there has been much interest in the γ-alkylation of α,β-unsaturated carbonyl compounds and their derivatives. Unsaturated esters,[1] ketones,[2] enamines,[3] aldimines[4] and acids[5,6] have been studied. The elaboration of polyisoprenoid compounds has also been the focus of numerous studies owing to the crucial role of polyisoprenoids in many biological systems.[6] In a preliminary communication [6] we described the elaboration of a Z-isoprenoid unit in the synthesis of nerol **2** by means of the γ-alkylation of 2-butynoic acid. In this paper we describe the synthesis of various isomers of farnesol by means of two different isoprenoid homologations; the γ-alkylation of 2-butynoic acid, and the γ-alkylation of 3-methyl crotonic acid.

In the first route, the dianion of 2-butynoic acid was generated as previously described,[6] with some modifications; the dianion can be generated by using lithium diisopropylamide as well as lithium 2,2,6,6-tetramethylpiperidide, and it is important to allow the deprotonation to proceed for at least 1 h to minimize the formation of dialkylated material upon the addition of the isoprenyl bromide. In the case of the reaction of **1a** with **3**, the dialkylated material appears to be 2,2-bis(neryl)-but-3-ynoic acid (IR: 3330, 640 cm^{-1} assigned to the acetylenic hydrogen vibrations, 1750 cm^{-1} assigned to the ester function; NMR: a singlet at $\delta = 2.33$ assigned to the acetylenic proton, a correct integration for six vinyl methyl groups to one methoxy group), arising from the α-alkylation of the dianion of the free acid of **5**. We speculate that this dianion is formed if some lithium amide is still present when the alkylation starts, but that this dianion is not generated by **1a**.

The alkylation of **1a** affords both the γ-alkylation product (**4** after esterification) and the α-alkylation product (**5** after esterification), in the ratio of about 3:1. These two isomers cannot be readily separated, so the allene **5** is decomposed to the ketone **6** by treatment with morpholine[7] in ether or benzene, followed by acid work-up. The desired ene-yne-ester **4** can be separated from the keto-ester **6** by column chromatography. Treatment of **4** with lithium dimethyl cuprate and methylcopper[8] yields **7**, which is reduced to Z,Z-farnesol **8** with aluminium hydride.[9]

The ene-yne-ester **4** can be isolated in 30–40% yield calculated from the starting alcohol **2**. The final product, farnesol **8**, can be isolated in 20–25% yield (calc. from **2**), in 90–95% isomeric purity. The transformations described in Scheme 1 can equally well be applied to the 2,E isomer of **2** (**2a**, geraniol), to yield **4a**, the 6,E isomer of **4**. The yield of **4a** is comparable to that of **4** (33%), as is its isomeric purity (95%). In larger synthetic runs, the mixture of **4** and **6** can be excessively massive, requiring many kilograms of silica for column chromatography. To reduce the mass of material, the mixture is treated with Girard's reagent T to form a very polar and partially water-soluble derivative of **6**. This reduces the weight of the mixture containing **4**, and allows a less cumbersome column chromatographic isolation of **4**.

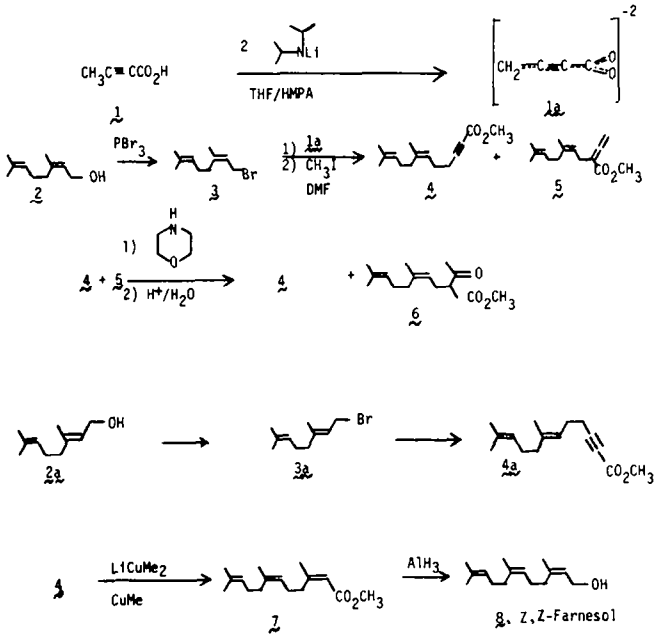
The second route of isoprenoid homolagation that was used involves the γ-alkylation of 3-methylcrotonic acid **9**, thereby allowing a one-step homologation of the entire isoprenoid skeleton.

When the dianion **9a** was treated with 1-bromo-3-methyl-2-butene **10**, the three products **11**, **12**, and **13** were found (GC) in the ratio 1:4:11. Thus the ratio of γ:α alkylation was 0.44:1.

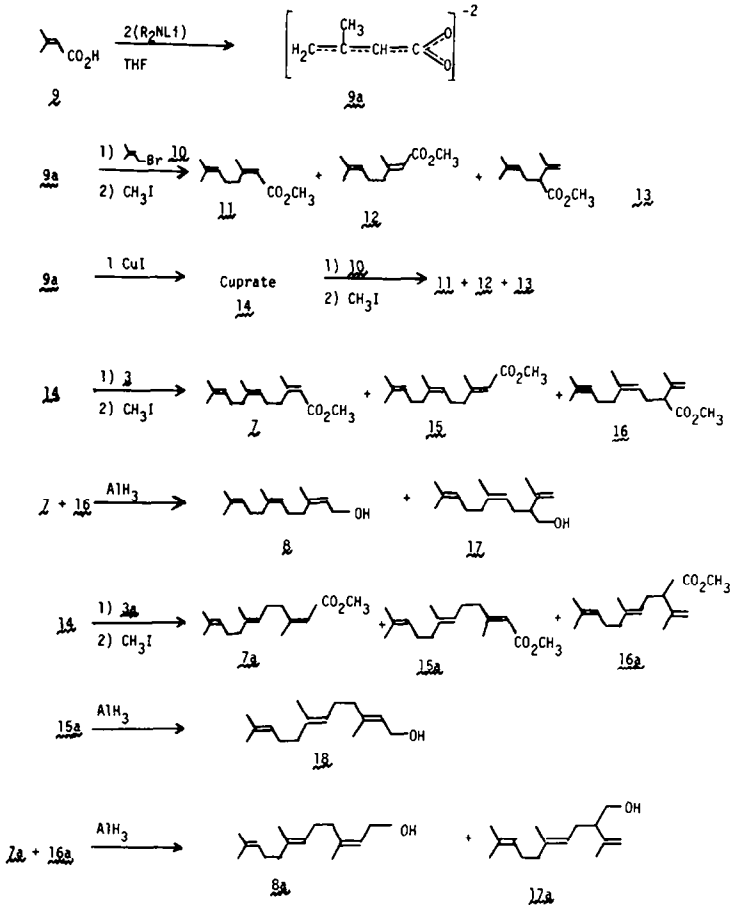
The ratio of γ-alkylation to α-alkylation was changed markedly by the addition of Cu^{I} to the dianion solution before alkylation. A molar equivalent of CuI was added, and the reaction mixture was permitted to warm to −40°, generating the cuprate **14**. The alkylating agent **10** was then added, and the reaction mixture was warmed to −20°. After 2 h at −20°, and methylation with DMF/MeI, a typical reaction work-up[10] was used to isolate the mixture of **11**, **12** and **13**. The ratio of products (GC) was 1:2.2:1.5. Thus the ratio of γ:α alkylation was 2:1. This represents a five fold increase in the γ:α ratio due to the complexation of Cu^{I}. Crumrine and Katzenellenbogen[11] noted a much greater ratio of γ:α alkylation (13:1) in the reaction between the cuprate complex of the same dianion with allyl bromide. No doubt allylic transposition (Sn2') of the allyl bromide contributes to the greater γ:α alkylation ratio.[1] When the same reaction was run with the cuprate **14** and neryl bromide **3**, the ratio of products was slightly different: **7**:**15**:**16** = 2.5:1.8:1. The ratio of γ to α-alkylation was therefore 4.3:1. When **14** was treated with geranyl bromide **3a**, the product ratio was **7a**:**15a**:**16a** = 2.5:2.1:1 (γ:α = 4.6:1). Thus the higher molecular weight bromides allow up to 80% γ-alkylation of the cuprate **14**.

The fact that γ-Z alkylation slightly exceeds γ-E alkylation when C_{10} allyl bromides are used suggests that **14** may exist in a cyclic form. In order to try to maximize

[a]Parts of this paper were presented at the 170th National Meeting of the American Chemical Society (see Ref. 5a).



Scheme 1.



Scheme 2.

γ-E alkylation in the reaction of **14** with **3a**, two moles of CuI were added to the dianion **9a**. Addition of **3a** followed by the same work-up gave almost the same ratio of products as observed when one mole of CuI was used. γ-Z **7a**: γ-E **15a**: α **16a** = 2.3:1.5:1, but the mass recovery of material in this case was somewhat lower than when one mole of CuI was used.

An obvious drawback to this alkylation of methylcrotonic acid is that three isomers are formed. In each reaction there is a γ-E product (**15** and **15a**), as well as γ-Z (**7** and **7a**) and α (**16** and **16a**) products. Low pressure column chromatography successfully separates the γ-E product from an inseparable mixture of γ-Z and α material, although multiple chromatographic runs are necessary. The inseparable mixture of γ-Z and α-esters is then reduced (AlH_3) to the corresponding alcohols, which can be separated by careful low pressure column chromatography.

Structure determination of the product farnesols (**8**, **18**) was by elemental analysis, TLC, GC and NMR data. The products move as one spot with the corresponding isomers from commercial farnesol on TLC (9:1 PhH:EtOAc) and are eluted as one peak from GC with the corresponding commercial isomer. Under the GC conditions employed (*vide infra*), the isomers of farnesol eluted in the order Z,Z-farnesol (20.8 min); (2-Z, 6-E) farnesol (21.3 min); (2-E, 6-Z) farnesol (22.6 min) and E,E-farnesol (23.3 min). Each farnesol, **8**, **18** and **8a**, caused the augmentation of the proper peak when mixed with commercial farnesol and injected. The branched alcohols **17** and **17a** are more volatile, with a retention time of *ca.* 19.7 min.

The NMR spectrum of the synthesized E,E and Z,Z-farnesol was compared to that of the corresponding purified (teflon spinning band distillation) commercial material. The spectra of the natural and the synthesized material were identical. Furthermore, there was very good agreement with published data.[12] Shift reagent studies gave additional verification to the structural assignment. Use of a 1:2 ratio of $Eu(FOD)_3$ to farnesol (or geraniol or nerol) allows unequivocal identification of the stereochemistry at the C_{2-3} double bond. In geraniol, commercial purified (E,E) farnesol, and **18**, the protons at C_4 and C_5 make up an unresolved broad "singlet" at $\delta = 4.00$. In nerol, commercial purified (Z,Z) farnesol, and **8**, the C_5 protons are a quartet ($J = \sim 7$) centered at $\delta = 3.89$, and the C_4 protons are a triplet ($J = \sim 7$) centered at $\delta = 5.08$.

EXPERIMENTAL

NMR spectra were taken in $CDCl_3$ on a Varian A-60D and a Varian T-60, all at 60 MHz. Location of peaks (δ) is by parts per million away from TMS as an internal standard. $Eu(FOD)_3$ was used at about a 1:2 molar ratio of shift reagent to substrate (*ca.* 120 mg shift reagent for 50 mg substrate). IR spectra were recorded neat on NaCl plates, on a Beckman IR-12. TLC runs were on 7.6 cm. microscope slides covered with a 0.25 mm thickness of Woelm F silica, with a magnesium aluminum silicate binder. The solvents were PhH, and combinations of PhH and EtOAc, and PhH and Skelly B (SkB). Visualization of spots was by phosphomolybdic acid, 5% in EtOH (wt/vol) followed by heat. Gas chromatography was run on a 6 ft column of Carbowax-20M, 1.36% on Chromosorb W/HP in a Varian 1400, with a temperature program of 60°–200° at 4° min. Low Pressure Column Chromatography (LPCC) was run on Woelm silica (200–325 mesh). A Milton-Roy pump (120 pulses/min) was used at pressures of *ca.* 80 psi max. pulse pressure. Fractions (25 ml) were taken at 10–30 ml/min. Evaporations were done under reduced pressure at or below 35°. 3-Methylcrotonic acid (Baker) was suspended in dry PhH. The stirred mixture was then filtered, and the filtrate dried ($CaSO_4$), filtered, and evaporated to a solid. HMPA was stirred with CaH_2 (1 g/100 ml) overnight under N_2, then distilled at low pressure (80–82°/1.6–1.7 torr). It was stored under N_2 in serum-capped bottles in plastic bags. THF was distilled from CaH_2 or $LiAlH_4$ directly before use. Diisopropylamine was stirred overnight with CaO (1 g/30 ml) under N_2, filtered, and distilled at atmospheric pressure. It was stored over mossy zinc under N_2 in brown, serum-capped bottles in plastic bags. Cuprous iodide was purified by the method of Kaufman and Teter.[13] Organic solutions were dried with anh. $CaSO_4$. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All alkylations were run under N_2.

Alkylation of 2-butynoic acid

Methyl(6Z)-7,11-dimethyl-dodeca-6,10-dien-2-ynoate **4**. Nerol (35.9 g, 23.3 mmole, Fluka 98%) was placed in a 1 l single-neck flask protected from light and anhydrous ether (550 ml) was added. PBr_3 (9.63 ml, Aldrich, 99%) was added slowly. Upon completion of the addition, the solution was stirred at 25° for 30 min, then refluxed for 2 h.[14] It was then allowed to cool slightly and was poured onto ice (400 ml). Sat. NaCl (20 ml) was added and the organic layer was removed and saved. The aqueous layer was extracted with Et_2O (250 ml) and the organic phases were combined and washed with sat. $NaHCO_3$, sat. NaCl, and then dried (Na_2SO_4) for 1 h in the dark. After filtering, the filtrate was evaporated, leaving neryl bromide as a light yellow oil (50.6 g, 100%).

Into THF (1900 ml) was placed distilled 2,2,6,6-tetramethylpiperidine (99.1 ml). The mixture was cooled to −75°, and *n*-BuLi (233 ml, 2.4 N) was added, keeping the temperature at or below −60° (20 min). The mixture was cooled to −75° and stirred for 30 min, then cooled to −95° and a solution of 2-butynoic acid (23.6 g) dissolved in HMPA (325 ml) was added, keeping the temperature at or below −65° (~5 min). The mixture was stirred for 1 h at −80°, then cooled to −95° and the neryl bromide dissolved in THF (20 ml) was added, keeping the temperature at or below −75° (~2 min). The mixture was stirred at −75° for 2 h, then MeOH (125 ml) was added, and the mixture was warmed to 25°. The mixture was evaporated to a volume of ~900 ml, then DMF (550 ml) and CH_3I (153 ml) was added, with cooling. The reaction mixture was stirred under N_2 overnight, then poured into H_2O (3.5 l). The CH_3I layer was removed and the aqueous layer was extracted twice with pentane. All organic extracts were combined and washed with cold (0°) 3N HCl, then with $NaHCO_3$, and then with sat. NaCl. After drying, the solution was evaporated, leaving a dark yellow oil (53.1 g).

The oil was placed in a 1 l single-neck flask containing technical morpholine (227 ml) and benzene (300 ml). The mixture was stirred under N_2 for 2 h at 25°, then neutralized to pH7 (HCl). The neutralized solution was then placed in a sep. funnel and the org. layer was removed. The aqueous layer was extracted twice with *n*-pentane. All organic extracts were combined and washed with H_2O, then with sat. $NaHCO_3$, and with sat. NaCl. The solution was then dried, filtered, and then evaporated, giving an orange oil (45.2 g). Gravity column chromatography was performed using Merck CC-4 (3600 g) with a Skelly B eluent, followed by increasing amounts of PhH in the Skelly B. Some overlap between the ketone (eluted with 1:1 PhH:Skelly B) and the product (eluted with 1:4 PhH:Skelly B) was experienced and these overlap fractions (22.17 g of oil) were dissolved in hexane (10 ml) and injected onto a low pressure column of Merck CC-7. Elution was begun with 10% PhH/hexane and the product eluted in 30% PhH/hexane. The total yield was 19.4 g, 35.6% (93% pure by GC).

Methyl(Z,Z)-Farnesoate **7**. THF (1 l.) was charged into a 2 l. 3-necked round bottom flask fitted with a mechanical stirrer and a thermometer. CuI (73.8 g, 390 mmole) was added and the mixed suspension cooled to −30°. MeLi(1.8 M in Et_2O, 700 mmole) was added carefully, keeping the reaction temperature at or below 0°. After the addition, the mixture (containing 312 mmole $LiCuMe_2$ and 78 mmole CuMe) was cooled to −70°. **4** (9.1 g, 38.9 mmole) was added in dry THF (75 ml). The reaction proceeded at −70° for

6 h. Then MeOH (25 ml) in Et_2O (50 ml) was added, keeping the temperature at or below −60°. Then MeOH (25 ml) (neat) was added, the reaction was warmed to *ca.* 0°, and poured into a mixture of sat. aq. NH_4Cl (1.5 l.) and pentane (500 ml). After mixing and standing 1 h, the mixture was filtered and the solid washed three times with pentane. The filtrate and washes were combined; the organic and aq. phases were separated. The aq. phase was washed with pentane; the organic fraction was combined with the pentane wash, and this phase was washed with H_2O, and then with sat. NaCl. The organic phase was evaporated to an oil, which was applied to LPCC (25 mm × 2 m, PhH-EtOAc eluants with increasing amounts of EtOAc: 10%, 20%, 50%). The product **7** was isolated (6.05 g, 24.2 mmole, 62%) as a chromatographically homogeneous oil.

Z,Z-Farnesol **8**. AlH_3 was generated by the method of Brown and Yoon;[9] $LiAlH_4$ (98.4 ml, 98.4 mmole), 1.0 M in THF (Alfa) was placed in a 500 ml 3-necked round bottom flask containing a magnetic stirrer and fitted with a thermometer and a syringe septum. The solution was cooled to −25°, and conc. H_2SO_4 (2.67 ml, 48.0 mmole) was added dropwise, keeping the temperature at or below +5°. After the addition was complete, the mixture was stirred at −10° for 30 min. The ester **7** (6 g, 24.0 mmole) was added, and the reaction allowed to proceed for 1.5 h. Ether (225 ml) was then added, followed by H_2O (4 ml, carefully dropwise), 15% NaOH in H_2O (4 ml), and finally H_2O (16 ml). The mixture was filtered, and the granular solid was washed with ether. The filtrate and wash were combined, dried, and evaporated to an oil, which was subjected to LPCC (25 mm × 2 m, PhH eluant followed by 5% EtOAc in PhH, then 10% EtOAc in PhH), yielding two fractions of Z,Z-farnesol. The purer fraction (1.20 g, 5.4 mmole, 22.5%) was 92.7% pure (GC); the more impure fraction (2.53 g, 10.6 mmole, 44.0%) was 77.5% pure (GC). Both fractions were at least 93% isomerically pure. NMR: 3-Me $\delta = 1.75$; 7-Me $\delta = 1.70$; 11-Me *trans* to CH_2 $\delta = 1.70$; 11-Me *cis* to CH_2 $\delta = 1.63$.

Methyl(6E)-7,11-*dimethyl-dodeca*-6,10-*dien*-2-*ynoate* **4a** was synthesized from geranyl bromide **3a** and 2-butynoic acid **1** exactly as described in the synthesis of **4**. Geraniol **2a** (100 g, 650 mmole) was converted to geranyl bromide, which was reacted with the dianion **1a** of 2-butynoic acid derived from the acid **1** (65.8 g, 784 mmole). After methylation, decomposition of the allene, and isolation of **4a**, the yield was 50.9 g (33.5% yield from geraniol) of 95% pure material.

Alkylation of 3-methylcrotonic acid

The reaction of 3-methylcrotonic acid dianion **9a** *with 1-bromo-3-methyl-2-butene* **10** *in the absence of* Cu^+; THF (200 ml) was charged into a 500 ml 3-necked round bottom flask, fitted with a dropping funnel, thermometer and a magnetic stirrer. 2,2,6,6-Tetramethylpiperdine (Aldrich, distilled and stored over mossy zinc, under N_2, in serum-capped bottles; 10.5 g, 74.5 mmole) was added and the mixture cooled to −70°. *n*-Butyl lithium (2.5 N in hexane, 29 ml, 72 mmole) was added. The reaction was cooled to −70°. The acid **9** (3.5 g, 35 mmole) was added as a solution in HMPA (35 ml). The temperature was kept at or below −60° during the addition. The mixture was cooled to −70°, and the bromide **10** was added all at once. After 30 min, MeOH (20 ml) was added, the reaction was warmed to room temperature, evaporated to *ca.* 80 ml, and diluted to 200 ml with DMF. Methyl iodide (40 ml) was added, and after 2 h at 25°, TLC (PhH solvent) showed no acid left. The work-up was the same as after the esterification step in the synthesis of **4**. An oil (5.26 g, theory for a yield of only **11**, **12** and **13** is 6.37 g) was isolated, which contained **11**, **12** and **13** in the ratio of 1:4:11 by GC. Structural assignment was by comparison of TLC, GC and NMR with **11** and **12** synthesized via Scheme 1.[6] The diagnostic NMR signal is that of the 3Me group of **11** and **12**.[6,12b] In **11**, the 3Me has $\delta = 1.90$, and in **12** the 3Me has $\delta = 2.18$. Methyl 2-(isopropenyl),5-methyl-hex-4-enoate **13** has the characteristic terminal vinyl absorption at $\delta = 4.90$, and the 5Me signal is at $\delta = 1.77$. The GC retention times are in the increasing order of **13**, **11**, **12**, and a mixture of **11** made by the two routes elutes as one peak. This is also true for **12**.

The reaction of the cuprate **14** *with* **10**. This reaction was run in the same manner as that of **9a** with **10**, with the following changes; 3-methylcrotonic acid **9** was added as a THF solution, not in HMPA, since the HMPA would complex with the Cu^+. After the generation of **9a**, the mixture was warmed to −40°, and CuI (one molar equivalent) was added. The mixture was warmed to −20°, then cooled to −70°, and **10** was added. After 2 h at −70° the material was warmed to 0° and worked up as above. The ratio of **11**:**12**:**13** was 1:2.2:1.5.

Methyl(2-Z,6-Z)-3,7,11-*trimethyl-dodeca*-2,6,10-*trienoate* **7**. Neryl bromide **3** was synthesized from nerol **2** (195 mmole, 30 g, Fluka 88% pure by GC) by the method of Osbond[14] and used within 2 h of synthesis: A 3-l Morton flask was fitted with a low temperature thermometer and a mechanical stirrer. THF (1 l) and diisopropylamine (62.7 ml, 45.3 g, 448 mmole) were charged into the system, and the mixture was stirred and cooled to −60°. *n*-Butyl lithium (in hexane, 483 mmole) was added. The mixture was stirred 30 min, at which time it had cooled to −70°. 3-Methylcrotonic acid **9** (21.4 g, 214 mmole) in dry THF(125 ml) was added carefully, keeping the reaction temperature at or below −55°. This mixture was then stirred for 1.5 h at −70°. CuI (37.1 g, 195 mmole) was then added, and the well stirred mixture was warmed to −15°, generating the cuprate **14**. The entire yield of neryl bromide **3** from the first paragraph of this preparation was then added in ether (~80 ml). This caused the temperature to rise to −5°. The reaction mixture was held at *ca.* −10° for 1.5 h. MeOH (50 ml) was then added, and the reaction mixture was evaporated to a syrup. Dry DMF (300 ml) was added, and the resulting solution was cooled to 10°. MeI (125 ml) was added, and the mixture was allowed to stand at 25° overnight. The reaction mixture was then poured into a mixture of sat. aq. NH_4Cl (1 l) and pentane (500 ml). After mixing, the three-phased system was filtered, and the solid was rinsed with pentane twice and discarded. The filtrate and washings were combined, and the organic and aq. phases were separated. The aq. phase was washed three times with pentane and discarded. The saved organic phase was combined with the pentane washings, and this organic solution was washed consecutively with cold 3N HCl, H_2O, dilute $NaHSO_3$, H_2O, sat. $NaHCO_3$ and sat. NaCl. The organic solution was then dried and filtered, and the solvent was removed by evaporation. A mobile oil (47.1 g) remained, containing 28% methyl Z,Z-farnesoate **7**, 20% methyl (2-E,6-Z) farnesoate **15**, 11% methyl (4-Z) 2-isopropenyl, 5, 9-dimethyl-deca-4,8-dienoate (α-alkylation product) **16** and small amounts of the other two methyl farnesoates.

The oil was separated by LPCC on a 50 mm × 1 m column, using 20% PhH 80% Skelly B eluent. This yielded 7.9 g of a mixture of **7** and **16**, and 16.9 g of a *ca.* 1:1 mixture of **15** and (**7** and **16**). Another fraction (3.4 g) of *ca.* 2:1 **15**: (**7** and **16**) was also isolated. Repeated rechromatography of these mixtures (2–25 mm × 1 m columns in series) permitted the isolation of another 4.3 g of a mixture of **7** and **16**, the total recovery of this mixture was 12.2 g, containing **7**:**16** in the ratio of 4:1.

Z,Z Farnesol **8**. The mixture of **7** and **16** isolated directly above was reduced with AlH_3 as described above for relatively pure methyl Z,Z-farnesoate, giving in this case a mixture of alcohols (**8** and **17**). The mixture of alcohols was separated by LPCC (2–25 mm × 1 m columns in series) using 5% EtOAc, 95% PhH. The branched alcohol **17** is eluted before the desired Z,Z-farnesol. The Z,Z-farnesol was isolated (20.2 mmole, 10% yield from nerol) as an oil containing trace amounts of 2-Z,6-E farnesol and methyl Z,Z-farnesoate (**8**:**8a**:**7** = 1:0.08:0.03). Anal. ($C_{15}H_{26}O$) C, H. Further purification of mixtures of **7**, **15** and **16**, followed by AlH_3 reduction and LPCC, allowed the isolation of a further 10.4 mmole (5.3% from nerol) of material with an isomeric purity of 90%.

E,E-*Farnesoic acid* **15a**. Geranyl bromide **3a** was synthesized from geraniol (195 mmole, Aldrich Gold Label, 94% pure by GC) by the method of Osbond[14] and used directly within 24 h of synthesis; the reaction and work-up was run exactly as described for the synthesis of **7** via **14**, through the LPCC separation of the γ-E isomer from a mixture of γ-Z and α-isomer. The oil (46·2 g) which was applied to the 50 mm column contained **16a** (16%), **7a** (39%), and the desired **15a** (34%), as well as traces of **7** and **15** (*ca.* 1.2% each). After repeated LPCC's using 7:3 SkB:PhH, a total of 12.8 g (51 mmol, 26% from **2a**) of **15a** (89% isomeric purity) was isolated.

E,E-*Farnesol* **18** was synthesized by the AlH_3 reduction of **15a**

as described for the synthesis of **8**. From 10.3 g (41.2 mmole) of **15a**, 5.18 g (26.1 mmole, 63.5%) of material with 88% isomeric purity was isolated. Anal. ($C_{15}H_{26}O$) C, H. In a separate run, 51 mmol of **15a** was reduced to give **18** in an isolated yield of 40.7 mmol (79%) of material with 87% isomeric purity. NMR: 3-Me $\delta = 1.68$; 7-Me $\delta = 1.60$; 11-Me *trans* to CH_2 $\delta = 1.68$; 11-Me *cis* to CH_2 $\delta = 1.60$.

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