Stereospecific Synthesis of (2*Z*,4*E*,6*E*)-3,7,11-Trimethyl-2,4,6,10-dodecatetraene [*trans*(C_{10})-Allofarnesene]

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The stereospecific synthesis of the title acyclic sesquiterpene, isolated from *Perilla frutscens* f. viridis Makino (Japanese name, Aojiso) by the palladium-catalyzed cross-coupling of 2-(4,8-dimethyl-1,3,7-nonatrienyl)-1,3,2-benzodioxaborole with (*Z*)-2-bromo-2-butene, is described. The benzodioxaborole was prepared by the hydroboration of 4,8-dimethyl-3,7-nonadien-1-yne, newly prepared *via* three steps from geranial, with 1,3,2-benzodioxaborole.

Two isomers, **1** and **2** of α-farnesene were isolated from *Perilla frutscens* Makino (Japanese name, Aojiso) by Sakai and Hirose, who called them *trans*(C_{10})-allofarnesene and *cis*(C_{10})-allofarnesene and assigned the structures, (2*Z*,4*E*,6*E*)-3,7,11-trimethyl-2,4,6,10-dodecatetraene and its (2*E*,4*E*,6*E*)-isomer.[1]

In this paper, a stereospecific synthesis of (2*Z*,4*E*,6*E*)-3,7,11-trimethyl-2,4,6,10-dodecatetraene (**1**) corresponding to *trans*(C_{10})-allofarnesene by the palladium-catalyzed cross-coupling of 2-(4,8-dimethyl-1,3,7-nonatrienyl)-1,3,2-benzodioxaborole (**7**) with (*Z*)-2-bromo-2-butene[2] is described. The synthesis is based on the method developed by us and reported in previous papers.[3,4]

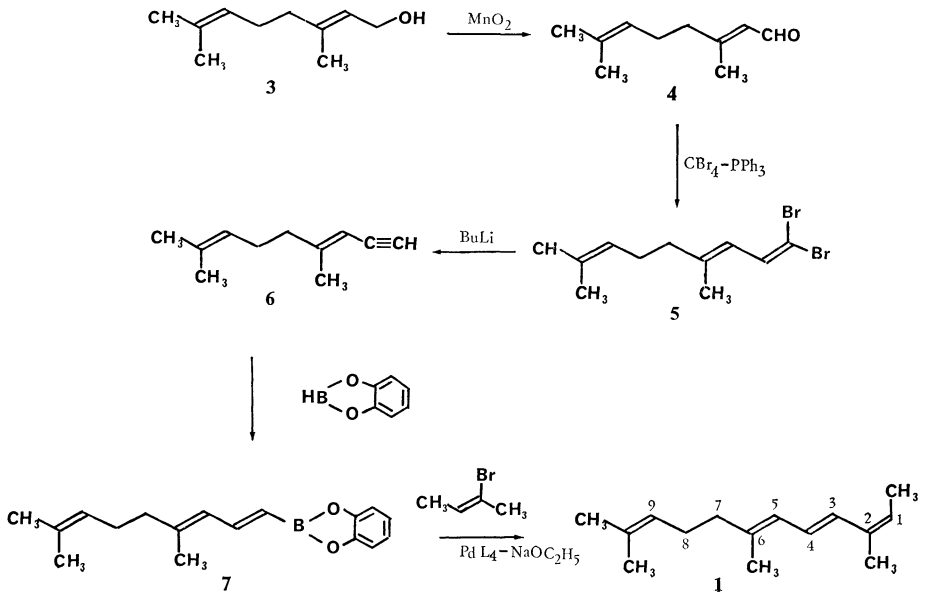
The alkenylborane, **7** required for the coupling reaction was prepared *via* three steps from geranial (**4**), itself previously prepared by the oxidation of geraniol (**3**) with active manganese dioxide.[5,6]

Thus, the reaction of geranial (**4**) with carbon tetrabromide and triphenylphosphine in dichloromethane in the presence of zinc, according to the method developed by Corey and Fuchs,[7] gave dibromide (**5**) in a 95% yield. Analysis by GC indicated that the geometry of geranial (**4**) was retained in dibromide, **5**, the ratio of (3*E*)- and (3*Z*)-isomer being 98:2. 4,8-Dimethyl-3,7-nonadien-1-yne (**6**) was prepared in a 90% yield by the reaction of dibromide, **5**, with butyllithium in hexane. The ratio of (3*E*)- and (3*Z*)-isomers in the product, **6**, was found by GC analysis to be 98:2.

The reaction of **6** with 1,3,2-benzodioxaborole[8] at 70 °C in an atmosphere of nitrogen gave 2-(4,8-dimethyl-1,3,7-nonatrienyl)-1,3,2-benzodioxaborole (**7**) as a viscous oil in a 72% yield. The ^{1}H NMR spectrum of borole, **7**, indicated that it was nearly a single isomer. It was found, however, that it gradually decomposed when exposed to air.

A mixture of borole **7** and (*Z*)-2-bromo-2-butene[2] in benzene containing $Pd(PPh_3)_4$[9] and sodium ethoxide was heated under reflux for 2 h in an atmosphere of nitrogen. The subsequent distillation of the product by Kugelrohr gave (2*Z*,4*E*,6*E*)-3,7,11-trimethyl-2,4,6,10-dodecatetraene (**1**) [*trans*(C_{10}) allofarnesene] in a 51% isolated yield. It was found that the use of THF as the solvent in this coupling considerably lowered the yield (29%) of **1** as well as the stereoselectivity of the coupling, the ratio of the (2*Z*,4*E*,6*E*) and (2*E*,4*E*,6*E*) isomers in the product being 32:68.[10]

The 200 MHz ^{1}H NMR spectrum of the synthetic *trans*(C_{10}) allofarnesene (**2**) thus obtained gave, for the



Scheme 1.

first time, well-resolved signals for all the olefinic protons and the methyl groups; their assignments are described in the Experimental section.

Experimental

The IR spectra were recorded on a Hitachi-Perkin Elmer Model 125 spectrometer. The ^{1}H-NMR spectra of all compounds with the exception of synthetic farnesene were determined with a Hitachi R-22 spectrometer (90 MHz) (solvent $CDCl_3$: TMS as the internal reference). The ^{1}H-NMR spectra of the synthetic farnesene was recorded with a JEOL JNM-FX-200 spectrometer (200 MHz). The mass spectra of **5** and **6** were determined with a JEOL JMS-D 300 spectrometer (70 eV) in the Faculty of Agriculture. Specimens for analysis were prepared by distillation with Kugelrohr (Shibata GTO-250 R). The bp shows the oven temperature of Kugelrohr. THF was distilled from benzophenone ketyl.

*Geranial (**4**).* This aldehyde was prepared by a procedure reported by Corey *et al.*[6] An analysis by VPC (10% Silicone OV-17 on Uniport B, 2m) indicated that this geranial contained 2% of neral (citral-b).

*Preparation of (3E)-1,1-Dibromo-4,8-dimethyl-1,3,7-nonatriene (**5**).* A mixture of PPh_3 (13.2 g, 50 mmol), CBr_4 (16.6 g, 50 mmol), and Zn powder (3.9 g, 60 mmol) in dry CH_2Cl_2 (250 ml) was stirred at room temperature for 48 h under an atmosphere of N_2. To this solution, we then added geranial (3.1 g, 20.5 mmol) in CH_2Cl_2 (10 ml) at 0 °C over a period of 15 min; the solution was stirred at that temperature for 1 h, after which the stirring was continued for another hour at room temperature. To the reaction mixture, we added hexane (500 ml) and colorless crystals and a viscous tarry material thus precipitated were removed by filtration. The removal of the solvent gave a mixture of products. This mixture was extracted with hexane (200 ml). The removal of the solid by filtration from the hexane solution and evaporation of the solvent gave a pale brown oil which was distilled with Kugelrohr to give dibromide, **5** (6.0 g, 95%); bp 80—85 °C(0.05 mmHg**). (Found: *m/z* 305.9643. Calcd for $C_{11}H_{16}Br_2$: M, 305.9621); MS *m/z* (rel intensity) 310 (M^++4, 0.2), 308 (M^++2, 0.4), 306 (M^+, 0.3), and 69 [$(CH_3)_2C{=}CH{-}CH_2^+$, 100]; n_D^{20}=1.5579; IR, (KBr disk), 1625, 1070, 845, and 775 cm^{-1}; ^{1}H NMR 1.60 (3H, s, 8-methyl), 1.68 (3H, s, 8-methyl), 1.74 (3H, s, 4-methyl), 2.08—2.12 (4H, m, 5 and 6-methylenes), 5.13 (1H, broad s, 7H), 5.90 (1H, broad d, J=10 Hz, 3-H), and 7.16 (1H, d, J=10 Hz, 2-H).

*Preparation of 4,8-Dimethyl-3,7-nonadien-1-yne (**6**).* To a solution of **5** (5.4 g, 17.5 mmol) in dry THF (30 ml) kept at −78 °C, was added dropwise BuLi in hexane (1.5 mol dm^{-3} solution, 28 ml, 42 mmol) over a period of 20 min; the solution was then stirred for 1 h at that temperature. The bath temperature was then gradually raised up to room temperature over the period of 1 h. After the solution had been further stirred for 1 h at room temperature, a saturated solution of NH_4Cl (5 ml) was added. The aqueous layer was separated and extracted with petroleum ether. The combined extracts were washed with saturated brine and with water and dried over anhydrous $MgSO_4$. The distillation of the product by Kugelrohr gave 4,8-dimethyl-3,7-nonadien-1-yne (**6**) (2.35 g, 90%); bp 75 °C (15 mmHg). (Found: *m/z* 148.1223. Calcd for $C_{11}H_{16}$: M, 148.1250); MS *m/z* (rel intensity) 148 (M^+, 0.4), 133 (M^+-CH_3, 8), and 69 [$(CH_3)_2C{=}CH{-}CH_2^+$, 100] n_D^{20}=1.4838; IR (film), 3296(C≡CH), 2104(C≡C), and 1632 cm^{-1}; ^{1}H NMR, 1.60 (3H, s, 8-methyl), 1.68 (3H, s, 8-methyl), 1.91 (3H, s, 4-methyl), 1.09—2.13 (4H, m, 5- and 6-methylene), 3.02 (1H, t, J=2 Hz, 1-H), 5.11 (1H, broad s, 7-H), and 5.32 (1H, broad s, 3-H).

*2-(4,8-Dimethyl-1,3,7-nonatrienyl)-1,3,2-benzodioxaborole (**7**).* A mixture of **7** (0.45 g, 3.0 mmol) and 1,3,2-benzodioxaborole (0.33 ml, 3.0 mmol) was heated at 70 °C for 3 h under an atmosphere of N_2: Distillation by using Kugelrohr gave trienylborane, **7**, as a viscous oil, bp 130 °C (0.05 mmHg) (0.58 g, 72%). A shorter reaction time (1 h) resulted in a lower yield (37%) of the borane. This borane was used immediately for the next step. This trienylborane has been found to decompose gradually when it is exposed to air, but it can be stored in an atmosphere of N_2 in a refrigerator. ^{1}H NMR, 1.63 and 1.70 (each 3H, s, *gem*-dimethyl), 1.94 (3H, s, 6-methyl), 2.15—2.20 (4H, m, 4- and 5-methylenes), 5.17 (1H, broad s, 3-H), 5.80 (1H, d, J=18 Hz, 9-H), 6.14 (1H, broad d, J=11 Hz, 7-H), 7.07—7.34 (4H, m, aromatic protons), and 7.73 (1H, dd, J=18 and 11 Hz).

(Z)-2-Bromo-2-butene. This bromide was prepared in an 80% yield according to the method reported by Bordwell and Landis.[2] It showed bp of 44 °C(160 mmHg) [lit,[2] bp 83.5—84.0 °C]. The isomeric purity of the product was found to be 99% by GC analysis (Hitachi K-53 instruments, SVS capillary column, 0.25 mm×45 m, Ucon Oil LB-550X). This bromide was immediately used for the next step, since it is gradually isomerized during storage in a refrigerator. After one-week storage, the isomeric purity went down to *Z*/*E* 91:9.

Synthesis of trans*(C$_{10}$)-Allofarnesene (**1**).* A mixture of $Pd(PPh_3)_4$ (0.033 g, 0.029 mmol), 2-(4,8-dimethyl-1,3,7-nonatrienyl)-1,3,2-benzodioxaborole (0.348 g, 1.43 mmol), and (*Z*)-2-bromo-2-butene (0.23 g, 1.7 mmol) in benzene (5 ml) containing 2 M-NaOEt†† in EtOH (2 ml) was heated under reflux for 2 h in an atmosphere of N_2. The unreacted borane was then removed by oxidizing with 3 M-NaOH (1 ml) and 30% H_2O_2 (0.3 ml) for 1 h at room temperature. The reaction mixture was extracted with 1:1 benzene–hexane, and the solution was washed with saturated brine and dried over anhydrous $MgSO_4$. Distillation of the product by Kugelrohr gave 0.15 g (51%) of *trans*(C$_{10}$)-allofarnesene (**1**); bp 70 °C(0.08 mmHg). It had n_D^{20}=1.5371. IR (KBr disk), 3040, 1640, and 955 cm^{-1}. ^{1}H NMR, (200 MHz), δ 1.61,††† 1.69,††† 1.80,††† and 1.85††† (each 3H, s, *gem*-dimethyl, 3-methyl, and 7-methyl groups), 1.74 (3H, d, J=7 Hz, protons on C_1), 2.10 (4H, broad s, C_8 and C_9 methylene protons), 5.11 (1H, broad s, 10-H), 5.41 (1H, q, J=7 Hz, 2-H), 5.97†† (1H, d, J=10 Hz, 6-H), 6.57 (1H, d, J=15 Hz, 4-H), 6.42 (1H, dd, J=10 and 15 Hz, 5-H). UV, λ_{max} (C_2H_5OH) 270 nm (inflection, ε 33700), 280 (ε 39500), and 291 (ε 33000); MS, *m/z* 204 (M^+). The yield of *trans*(C$_{10}$)-allofarnesene in this coupling, examined by GLC (Hitachi 163 instrument with a 2 m in 15% Ucon Oil HB-2000 on Uniport B column and with tetradecane as the internal standard), was 89% (1.27 mmol), accompanied by 6% (0.086 mmol) of *cis* (C$_{10}$)-allofarnesene.

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** 1 mmHg≈133.322 Pa.

†† 1 M=1 mol dm^{-3}.

††† A further small splitting (J=1 Hz) due to a long-range coupling is observed in this signal.

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10) The observed lower stereoselectivity, when THF was used as the solvent, is probably due to the partial isomerization of (*Z*)-2-bromo-2-butene to its (*E*)-isomer before the coupling. The rate of the oxidative addition of the (*E*)-isomer to Pd(0) would probably be faster than that of the (*Z*)-isomer, since we observed that, in the cross-coupling reaction of a 1:1 mixture of (*E*) and (*Z*)-isomers of styryl bromide with (*E*)-1-hexenyl-1,3,2-benzodioxaborole catalyzed by $Pd(PPh_3)_4$, the rate of the disappearance of (*E*)-styryl bromide was some 10 times faster than that of the (*Z*)-isomer (unpublished results).