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Studies on Monoterpene Glucosides and Related Natural Products. XLV.[1] Synthesis of ^{13}C-Labeled Acyclic Monoterpenes for Studies on the Mechanism of the Iridane Skeleton Formation in the Biosynthesis of Iridoid Glucosides

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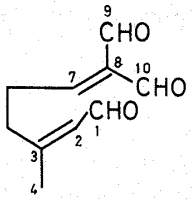
For studies on the cyclopentane ring formation from acyclic monoterpenes in the biosynthesis of iridoid glucosides, the following ^{13}C-labeled precursors of the acyclic monoterpene series were synthesized: [9-^{13}C]- and [4-^{13}C]-10-hydroxygeraniol (**9**), [2-^{13}C]-9,10-dihydroxygeraniol (**10**), (*R*)-(+)- and (*S*)-(−)-[9-^{13}C]-10-hydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**8**), (*R*)-(+)- and (*S*)-(−)-[8-^{13}C]-9,10-dihydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**11**).

Keywords——iridoid glucosides; biosynthesis; ^{13}C-labeled acyclic monoterpene precursors; 10-hydroxygeraniol; 9,10-dihydroxygeraniol; 10-hydroxycitronellol; 9,10-dihydroxycitronellol; synthesis

Two mechanisms have been proposed for the process of iridane skeleton formation from acyclic monoterpenes in the biosynthesis of iridoid glucosides. For glucosides of the secoiridoid series, a mechanism passing through 9,10-dioxoneral (**1**) and iridotrial (**2**) has been suggested. The randomization of the terminal carbons (C-9 and 10) of the acylic terpene in positions 3 and 11 of the formed iridoids is a feature of this route.[2] However, in regard to iridoid glucosides having certain groups such as a methyl group on C-4, a route passing through 10-oxogeranial (**3**), or 10-oxoneral (**4**), and iridodial (**5**) was demonstrated. Retention of the non-equivalency of the terminal carbons throughout the pathway[3] is characteristic of



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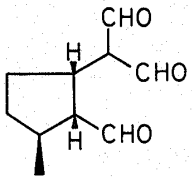

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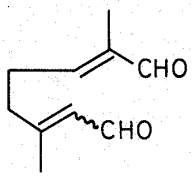
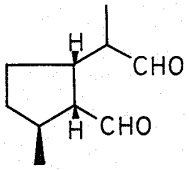


3 : (2*E*, 7*E*)-form
4 : (2*Z*, 7*E*)-form



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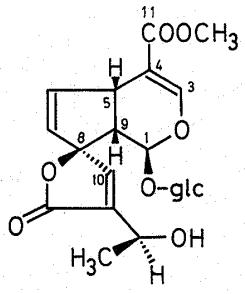

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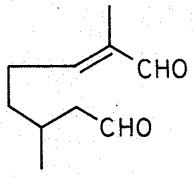

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Fig. 1

this route. On the other hand, for an iridoid glucoside plumieride (**6**), a route *via* 10-oxocitronellal (**7**) (equivalent to 10-hydroxycitronellol (**8**)) and iridodial (**5**) was once proposed.[4] This, however, was disproved at least for substances of the secoiridoid series.[2,5]

Administration of the following labeled acyclic terpenes with two and three hydroxy groups, which are regarded as equivalent to the corresponding di- and trialdehydes, to a plant in various combinations and tracing their fates could be a suitable method for detailed examination of the mechanism of iridane skeleton formation: 10-hydroxygeraniol (**9**), 9,10-dihydroxygeraniol (**10**), 10-hydroxycitronellol (**8**) and 9,10-dihydroxycitronellol (**11**). Many technical difficulties can be anticipated in carrying out feeding experiments with these radio-labeled compounds to a plant. However, the recent success[6] in obtaining high iridoid glucoside-producing cell suspension cultures of *Gardenia jasminoides* f. *grandiflora* in this laboratory enabled us to attempt administration of these compounds labeled with ^{13}C to the cell cultures.

This paper describes the synthesis of the above compounds labeled with ^{13}C for the purpose of feeding experiments.

For the synthesis of the above-described four labeled acyclic terpenes, the following conditions should be satisfied. i) Since they are to be administered to cell cultures in various combinations, the ^{13}C label should be introduced at a different position of the skeleton of each compound. ii) With regard to 10-hydroxygeraniol (**9**) and 10-hydroxycitronellol (**8**), it is necessary, at least, to have a compound labeled at either C-9 or C-10 with ^{13}C, so that the scrambling of the terminal groups as mentioned above can be examined. iii) With regard to substances of the citronellol-series, synthetic methods for labeling each of the enantiomers should be established. These could also be employable in other experiments using different plants.

In order to satisfy these conditions, we attempted to label 10-hydroxygeraniol (**9**) at the C-4 and C-9 positions separately, 9,10-dihydroxygeraniol (**10**) at the C-2 position, (*R*)-(+)- and (*S*)-(−)-10-hydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**8**) at the C-9 position, and (*R*)-(+)- and (*S*)-(−)-9,10-dihydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**11**) at C-8 position. According to the preparative methods established by experiments using non-labeled compounds, these ^{13}C labeled compounds were synthesized as follows.

i) Synthesis of [9-^{13}C]-10-Hydroxygeraniol (9)

Successive treatment of (carboethoxymethylene)-triphenylphosphorane (**12**) with $^{13}CH_3I$ and aqueous NaOH gave (α-carboethoxy[*methyl*-^{13}C]ethylidene)-triphenylphosphorane (**13**). Condensation of the latter with (*E*)-6-acetoxy-4-methyl-4-hexenal (**14**) obtained through ozonolysis of geranyl acetate (**15**) yielded the ^{13}C-labeled ester (**16**). As the observed chemical shift of the C-3 vinyl proton (δ 6.71, broad triplet, J=7.5 Hz) in the ^1H nuclear magnetic resonance (NMR) spectrum of the ^{13}C-labeled ester (**16**) was in accord with the chemical shift (δ

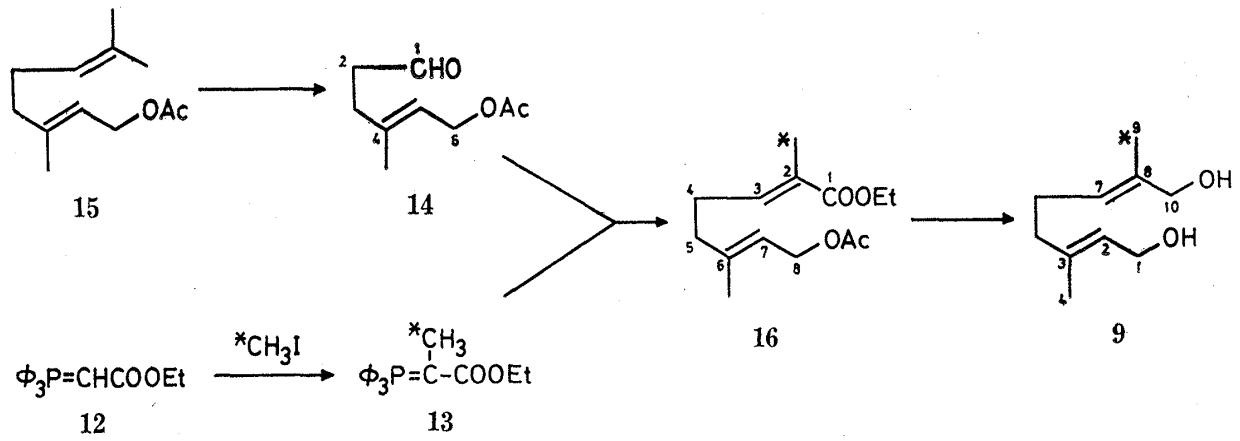

Fig. 2

6.58) of a vinyl proton calculated according to Pascual's equation[7,8] and that (δ 6.72)[9] of methyl (*E*)-2-methyl-2-pentenoate, the ester was assumed to be an (*E*)-form, *i.e.*, ethyl (2*E*, 6*E*)-8-acetoxy-2,6-dimethyl-2,6-octadienoate (**16**). The appearance of the signal of protons of the [^{13}C]methyl group at δ 1.82 (double doublet, $^1J_{H,C}$=127.8 Hz, $^4J_{CH_3,H-3}$=1.0 Hz) corroborated the location of ^{13}C at the 2-methyl group. Reduction of [2-*methyl*-^{13}C]-**16** with AlH_3 gave [9-^{13}C]-10-hydroxygeraniol (**9**). The ^{1}H NMR spectrum of this substance showed a double doublet of the [^{13}C]methyl protons at δ 1.64 ($^1J_{H-9,C-9}$=126.0 Hz, $J_{9,7}$=1.0 Hz), a broad singlet of two hydroxy protons at around δ 3.50, which disappeared on treatment with D_2O, and signals of two C-2 and C-7 vinyl protons at around δ 5.25—5.49. In its ^{13}C NMR spectrum, the signal at δ 21.19 corresponding to the C-10 signal of [10-^{13}C]-9-hydroxygeraniol showed almost no ^{13}C enrichement, while the signal at δ 13.74 attributable to the C-9 carbon of [9-^{13}C]-10-hydroxygeraniol (**9**) showed remarkable enrichment.[10] All these results indicated that this substance is [9-^{13}C]-**9**. The overall yield from the aldehyde (**14**) to [9-^{13}C]-**9** was 59%.

ii) Synthesis of [4-^{13}C]-10-Hydroxygeraniol (9)

4-Tetrahydropyranyloxybutanol (**17**) obtained by the reaction of 1,4-butanediol with one mol equivalent of 2,3-dihydropyran in the presence of pyridine–TsOH complex (PPTS)[11] was oxidized with pyridinium dichromate (PDC)[12] to afford 4-tetrahydropyranyloxybutanal (**18**), which was then condensed with phosphorane (**13**) to give the ester (**19**). The ^{1}H NMR spectrum of **19** showed a broad triplet (J=7.5 Hz) of the vinyl proton at δ 6.76 indicating it to be an (*E*)-form. On removal of the tetrahydropyranyl group, **19** yielded ethyl (*E*)-6-hydroxy-2-methyl-2-hexenoate (**20**), whose hydroxy group was oxidized with PDC to give the corresponding keto ester (**21**). Condensation of **21** with $^{13}CH_3MgI$ gave ethyl (*E*)-6-hydroxy-2-methyl-2-heptenoate (**22**). The ^{1}H NMR spectrum of this substance showed a double doublet ($^1J_{H-7,C-7}$=125.5 Hz, $J_{7,6}$=6.5 Hz) due to protons of the [^{13}C]methyl group at δ 1.21 and a sextet (J=6.5 Hz) due to the proton on the hydroxy-bearing carbon at δ 3.79. Thus, ^{13}C was evidently introduced into the position corresponding to C-4 of the desired substance, 10-hydroxygeraniol (**9**). Jones oxidation of [7-^{13}C]-**22** gave a ketone (**23**), which was condensed with diethyl ethoxycarbonylmethylphosphonate (**24**),[13] prepared from diethylphosphite, in the presence of NaH to give diethyl 2-methyl-1,5-heptadiene-1,6-dicarboxylate (**25**). The ^{1}H NMR spectrum of **25** showed a pair of double doublets ($^1J_{H,C}$=127.0 Hz, $^4J_{CH_3,H-1}$=1.2 Hz) due to the 2-[^{13}C]methyl protons of the (1*E*, 5*E*)- and (1*Z*, 5*E*)-forms at

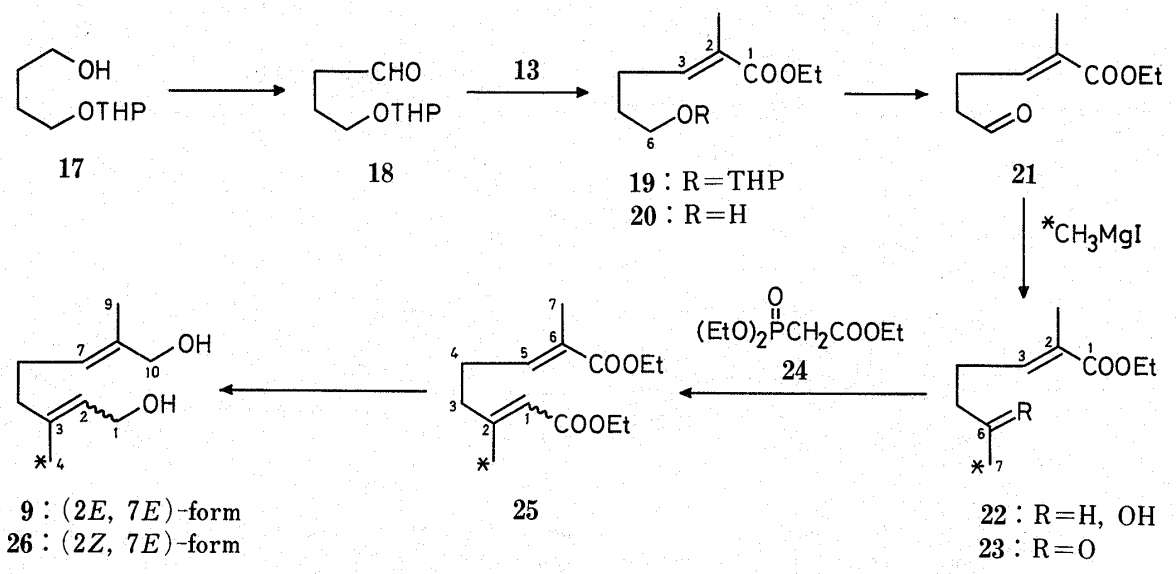

Fig. 3

δ 2.17 and 1.93, respectively, in a ratio of 4: 1.[14] Finally, reduction of [2-*methyl*-^{13}C]-**25** with AlH_3 yielded a mixture of [4-^{13}C]-10-hydroxygeraniol (**9**) and [4-^{13}C]-10-hydroxynerol (**26**) in a ratio of 4: 1. The ^{1}H NMR spectrum of the mixture showed a pair of doublets ($^1J_{H-4,C-4}$= 125.5 Hz) due to the ^{13}C-4 methyl protons of the (2*E*, 7*E*)- (**9**) and (2*Z*, 7*E*)-forms (**26**) at δ 1.66 and 1.77, respectively, and a broad singlet due to two hydroxy protons at around δ 2.30, which disappeared on treatment with D_2O. The overall yield from aldehyde (**21**) to the mixture of [4-^{13}C]-**9** and [4-^{13}C]- **26** was 66%.

iii) Synthesis of [2-^{13}C]-9,10-Dihydroxygeraniol (10)

5-Iodopentan-2-one (**27**)[15] obtained through decarboxyhalogenation of α-acetyl-γ-butyrolactone (**28**) with HI was subjected to $NaBH_4$ reduction followed by acetylation to give 2-acetoxy-5-iodopentane (**29**). Condensation of triphenylphosphonium iodide (**30**), derived from **29** and triphenylphosphine, with bis(tetrahydropyranyloxy)acetone (**31**), derived from dihydroxyacetone (**32**), in the presence of *n*-BuLi yielded 6,6-bis(tetrahydropyranyloxymethyl)-5-hexen-2-ol (**33**), which was further converted to the ketone (**34**) by oxidation with PDC. Subsequently, this substance was condensed with diethyl ethoxycarbonyl[^{13}C]-methylphosphonate (**24**),[13] which had been labeled by using $^{13}CH_3I$, in the presence of NaH. The ^{1}H NMR spectrum of the condensation product showed a pair of double doublets ($^3J_{H-4,C-2}$ =5.0 Hz, $J_{4,2}$=1.2 Hz) due to the C-4 methyl protons of ethyl 9,10-bis(tetrahydropyranyloxy)-geranate (**35a**) and the corresponding nerate (**35b**) at δ 2.15 and 1.87, respectively in a ratio of 4: 1, along with a broad doublet ($^1J_{H-2,C-2}$=159.0 Hz) of the ^{13}C-2 vinyl proton at δ 5.64. These observations indicated that ^{13}C was introduced through the above-mentioned condensation at the desired C-2 position. Reduction of the mixture of [2-^{13}C]-**35a** and [2-^{13}C]-**35b** with AlH_3 gave a product (**36a** and **36b**), which, through the removal of the tetrahydropyranyl group, yielded a mixture of [2-^{13}C]-9,10-dihydroxygeraniol (**10**) and [2-^{13}C]-9,10-dihydroxynerol (**37**) in a ratio of 4: 1. The ^{1}H NMR spectrum of the mixture showed a pair of broad

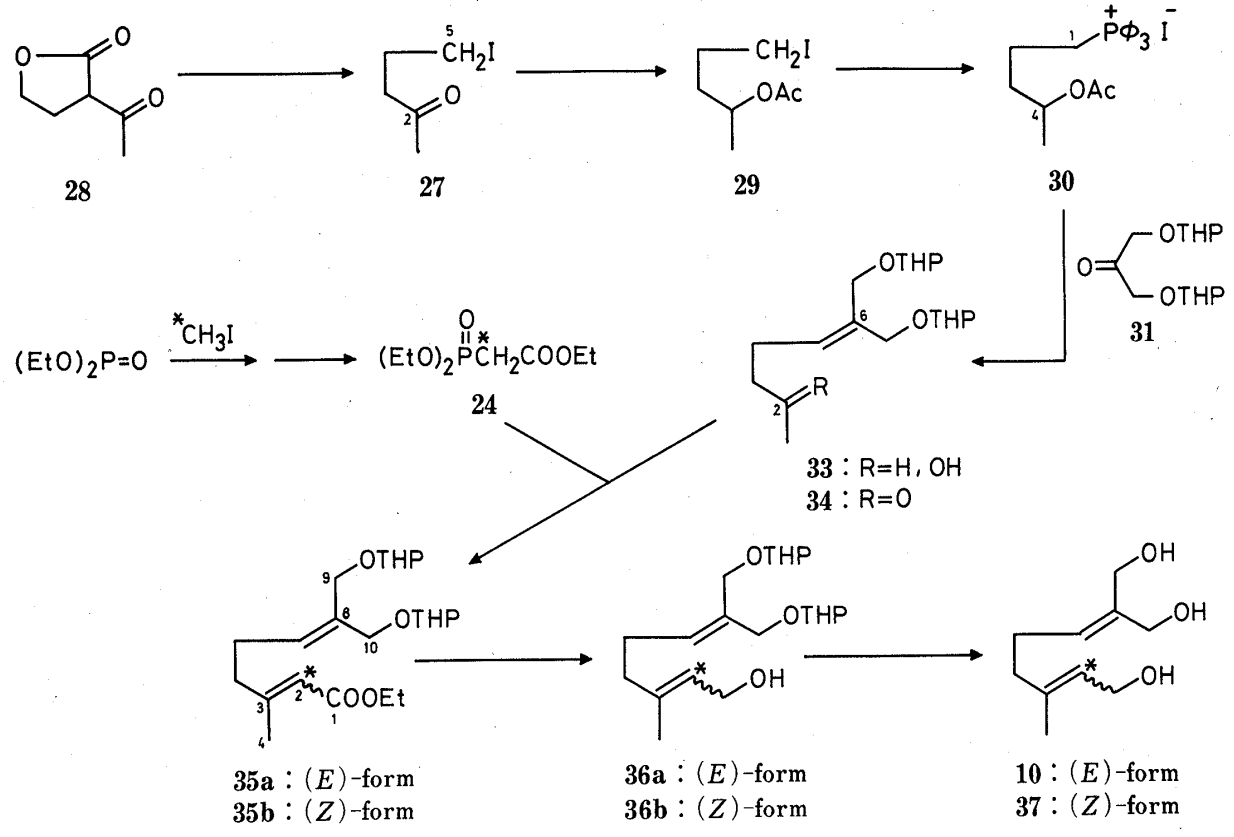

Fig. 4

doublets ($^3J_{H-4,C-2}$=5.0 Hz) due to the C-4 methyl protons of the (*E*)- (**10**) and (*Z*)-form (**37**) at δ 1.68 and 1.75, respectively, a broad singlet of the three hydroxy groups at around δ 1.80 which disappeared on treatment with D_2O, and a double triplet ($^1J_{H-2,C-2}$=152.0 Hz, $J_{2,1}$= 7.0 Hz) of the ^{13}C-2 vinyl proton at δ 5.36. The overall yield from the ketone (**34**) to the mixture of [2-^{13}C]-**10** and [2-^{13}C]-**37** was 68%.

iv) Synthesis of (*R*)-(+)-[9-^{13}C]-10-Hydroxycitronellol ((*R*)-(+)-8)

Acetylation of (*R*)-(+)-citronellol ((*R*)-(+)-**38**)[16] derived from (*R*)-(+)-pulegone (**39**) gave (*R*)-(+)-citronellyl acetate ((*R*)-(+)-**40**), $[\alpha]_D^{20}$ +3.51° ($CHCl_3$), which was further subjected to ozonolysis followed by reductive treatment with Zn–AcOH to yield (*R*)-(+)-6-acetoxy-4-methylhexanal ((*R*)-(+)-**41**), $[\alpha]_D^{20}$ +2.34° ($CHCl_3$). Condensation of the latter with ^{13}C-labeled phosphorane (**13**) gave ethyl (*E*)-(*R*)-(+)-8-acetoxy-2,6-dimethyl-2-octenoate ((*R*)-(+)-**42**), $[\alpha]_D^{20}$ +5.37° ($CHCl_3$). Its ^{1}H NMR spectrum showed a double triplet ($^3J_{H-3,C}$=7.5 Hz, $J_{3,4}$=7.0 Hz) of the C-3 vinyl proton at δ 6.75 and a broad doublet ($^1J_{H,C}$=128.0 Hz) of protons of the [^{13}C]methyl group at δ 1.83. It is thus evident that, through the condensation, ^{13}C was introduced into the desired position, which corresponds to the C-9 position of (*R*)-(+)-**8**, forming the product of (*E*)-configuration. Reduction of (*R*)-(+)-[2-*methyl*-^{13}C]-**42** with AlH_3 gave (*R*)-(+)-[9-^{13}C]-10-hydroxycitronellol ((*R*)-(+)-**8**), $[\alpha]_D^{20}$ +3.70° ($CHCl_3$). The ^{1}H NMR spectrum of this substance showed a broad doublet ($^1J_{H-9,C-9}$=125.5 Hz) of the ^{13}C-9 methyl protons at δ 1.64 and a broad singlet of two hydroxy protons at around δ 2.20, which disappeared on treatment with D_2O. Accordingly, this substance is (*R*)-(+)-[9-^{13}C]-**8**. The overall yield of (*R*)-(+)-[9-^{13}C]-**8** from (*R*)-(+)-aldehyde ((*R*)-(+)-**41**) was 85%.

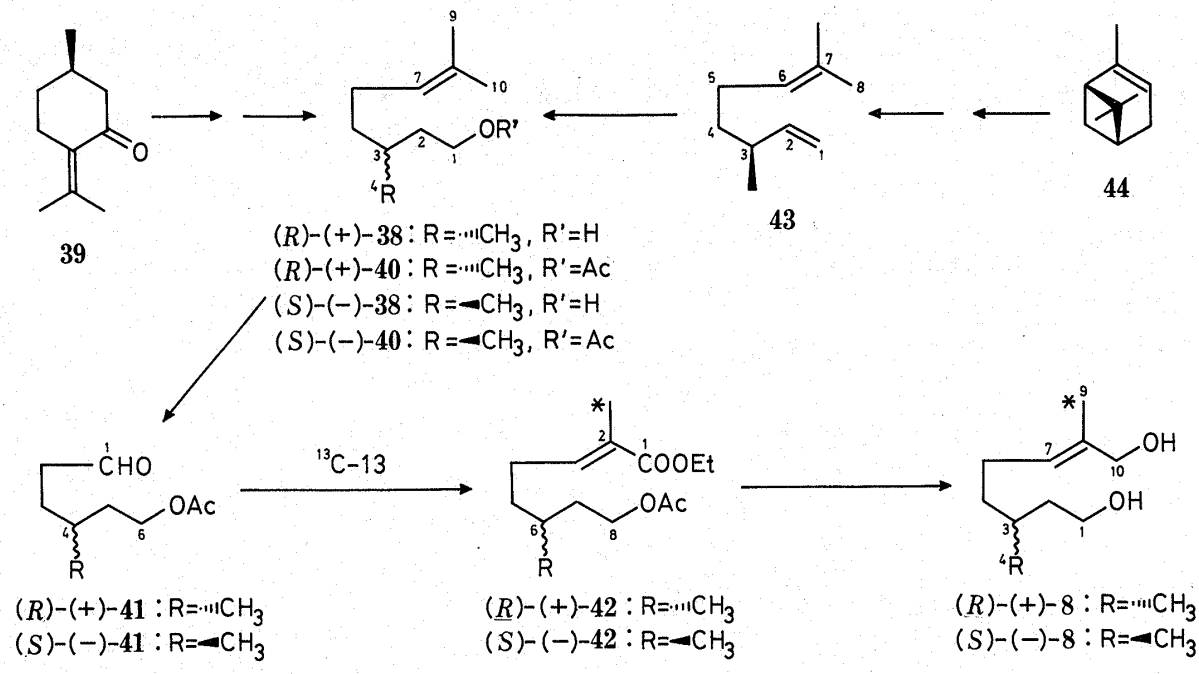

Fig. 5

v) Synthesis of (*S*)-(−)-[9-^{13}C]-10-Hydroxycitronellol ((*S*)-(−)-8)

Hydroboration of (*S*)-(−)-3,7-dimethyl-1,6-octadiene (**43**)[17] derived from (+)-α-pinene (**44**) yielded (*S*)-(−)-citronellol ((*S*)-(−)-**38**), $[\alpha]_D^{15}$ −4.09° ($CHCl_3$). (*S*)-(−)-Citronellyl acetate ((*S*)-(−)-**40**), $[\alpha]_D^{20}$ −3.43° ($CHCl_3$), derived from (*S*)-(−)-**38**, was subjected to ozonolysis to give (*S*)-(−)-aldehyde ((*S*)-(−)-**41**), $[\alpha]_D^{20}$ −2.19° ($CHCl_3$). Condensation of (*S*)-(−)-**41** with ^{13}C-labeled phosphorane (**13**) followed by reduction in the same way as for the synthesis of the above-described (*R*)-(+)-[9-^{13}C]-10-hydroxycitronellol ((*R*)-(+)-**8**) gave (*S*)-(−)-[9-^{13}C]-10-hydroxycitronellol ((*S*)-(−)-**8**), $[\alpha]_D^{20}$ −4.39° ($CHCl_3$).

vi) Synthesis of (R)-(+)-[8-^{13}C]-9,10-Dihydroxycitronellol ((R)-(+)-11)

Ozonolysis of (*R*)-(+)-citronellyl acetate ((*R*)-(+)-**40**) followed by reductive treatment with $NaBH_4$ gave (*R*)-(+)-6-acetoxy-4-methylhexanol ((*R*)-(+)-**45**), $[\alpha]_D^{20}$ +1.27° ($CHCl_3$), which, on tosylation followed by treatment with NaI, yielded (*R*)-(+)-1-acetoxy-6-iodo-3-methylhexane ((*R*)-(+)-**46**), $[\alpha]_D^{20}$ +8.54° ($CHCl_3$). After deacetylation, the product was converted into the tetrahydropyranyl ether ((*R*)-(+)-**47**). On the other hand, [2-^{13}C]-glycerol (**48**)[18] derived from diethyl [2-^{13}C]-malonate (**49**) was oxidized with hexabutyldistanoxane-Br_2[19] to give [2-^{13}C]-dihydroxyacetone (**32**). This substance was converted into the bis(tetrahydropyranyl) ether (**31**) and condensed in the presence of *n*-BuLi with (*R*)-(+)-phosphonium iodide ((*R*)-(+)-**50**) prepared from the above-described (*R*)-(+)-**47**. The resulting (*R*)-(+)-[8-^{13}C]-9,10-dihydroxycitronellol tris(tetrahydropyranyl) ether ((*R*)-(+)-**51**), $[\alpha]_D^{20}$ +2.37° ($CHCl_3$) gave (*R*)-(+)-[8-^{13}C]-9,10-dihydroxycitronellol ((*R*)-(+)-**11**), $[\alpha]_D^{20}$ +3.38° (EtOH) on removal of the tetrahydropyranyl groups. The ^{1}H NMR spectrum of this substance showed a broad singlet due to three hydroxyl groups at δ 2.84 which disappeared on addition of D_2O, broad doublets ($^2J_{H-10,C-8}=^2J_{H-9,C-8}=4.0$ Hz)[20] of the methylene protons on C-10 and C-9 at δ 4.16 and 4.26, respectively, and a broad triplet ($J=7.5$ Hz) of the C-7 vinyl proton at δ 5.49. Accordingly, it was confirmed that this substance is the desired (*R*)-(+)-[8-^{13}C]-**11**. The overall yield of (*R*)-(+)-[8-^{13}C]-**11** from (*R*)-(+)-**47** was 44%.

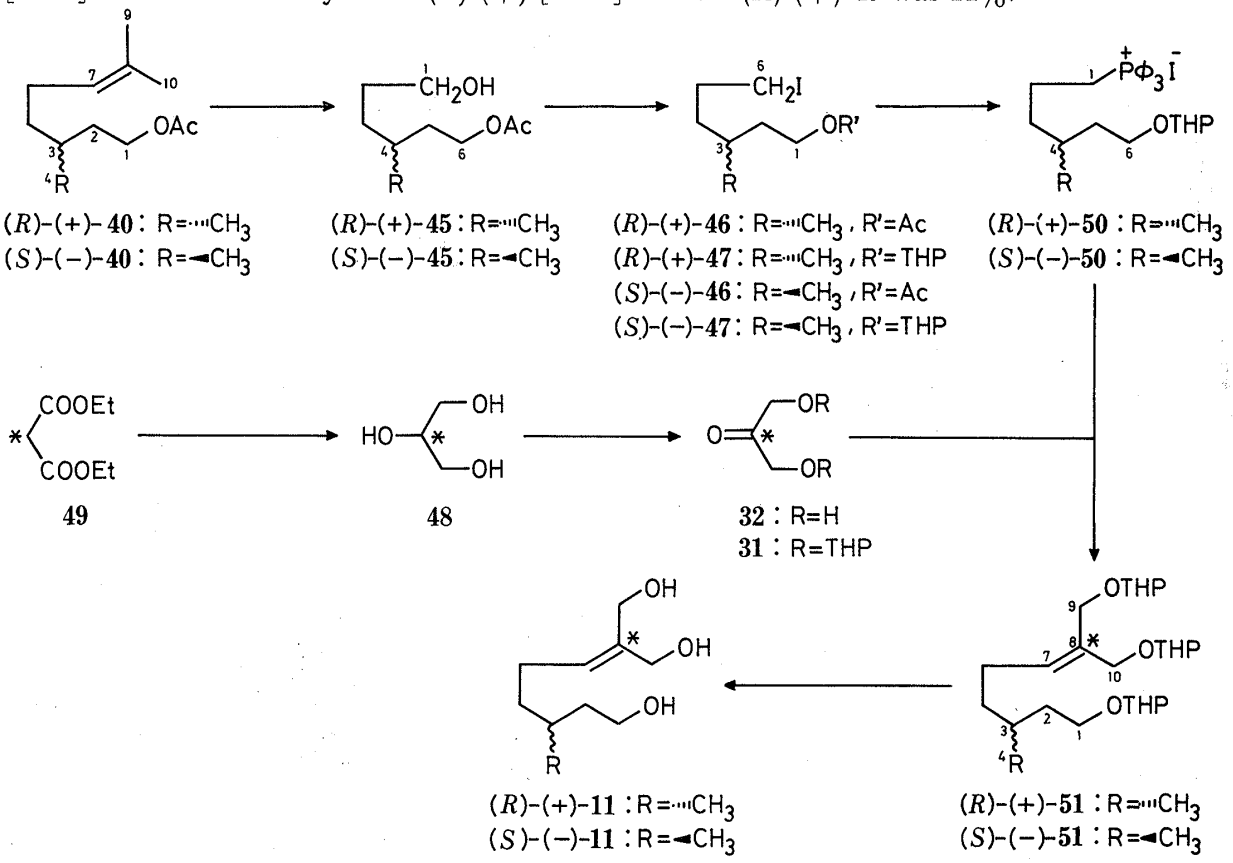

Fig. 6

vii) Synthesis of (S)-(—)-[8-^{13}C]-9,10-Dihydroxycitronellol ((S)-(—)-11)

Treatment of the (*S*)-(−)-alcohol ((*S*)-(−)-**45**), $[\alpha]_D^{20}$ −1.41° ($CHCl_3$), obtained through the ozonolysis of (*S*)-(−)-citronellyl acetate ((*S*)-(−)-**40**), in the same way as for the synthesis of (*R*)-(+)-[8-^{13}C]-9,10-dihydroxycitronellol ((*R*)-(+)-**11**) yielded (*S*)-(−)-[8-^{13}C]-9,10-dihydroxycitronellol ((*S*)-(−)-**11**), $[\alpha]_D^{20}$ −3.88° (EtOH).

Starting from $^{13}CH_3I$ (90 atom % ^{13}C) and diethyl [2-^{13}C]-malonate (**49**) (90 atom % ^{13}C), syntheses of labeled compounds with 90 atom % ^{13}C required for the administration experiments were thus accomplished.

As described above, [4-^{13}C]-10-hydroxygeraniol (**9**) and [2-^{13}C]-9,10-dihydroxygeraniol (**10**) thus obtained were still contaminated with some of the corresponding (*Z*)-forms. Each of the (*R*)-(+)- and (*S*)-(−)-forms of [9-^{13}C]-10-hydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**8**) and [8-^{13}C]-9,10-dihydroxycitronellol ((*R*)-(+)- and (*S*)-(−)-**11**) could also be contaminated with a small amount of the enantiomer. These stereochemical impurities, however, did not hinder the administration experiments, which will be described in a subsequent report. In order to carry out more precise experiments, we hope to prepare stereochemically pure precursors in the near future.

Experimental

General Procedures——Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Vacuum distillation was carried out by using a Büchi Kugelrohr apparatus and boiling points given here are the uncorrected temperatures inside the apparatus. Specific rotations were measured with a Union PM-101 automatic digital polarimeter. UV spectra were recorded on a Hitachi model 200-20 spectrophotometer and IR spectra on a Hitachi model 215 grating infrared spectrophotometer. ^{1}H NMR spectra were taken on a Varian A-60 or JEOL JNM-PMX 60 spectrometer in $CDCl_3$ and ^{13}C NMR spectra on a JEOL JNM-FX 100 FT-NMR spectrometer at 25.0 MHz or a JEOL JNM-FX 200 FT-NMR spectrometer at 50.2 MHz in $CDCl_3$ or CD_3OD with TMS as the internal standard. Of the ^{1}H NMR signals of ^{13}C-labeled compounds, only those coupled with ^{13}C are described. Low-resolution and high-resolution mass spectra were taken with a JEOL JMS-01SG-2 spectrometer. Column chromatography was performed on silica gel (silicic acid, 100 mesh, Mallinckrodt). Preparative thin layer chromatography (PLC) was carried out on silica gel plates (Kieselgel 60 PF_{254}, Merck, 20×20 cm, 1.0 mm thick) and, unless otherwise noted, the main band was scraped off and extracted with $CHCl_3$–MeOH (9: 1), then the extract was concentrated *in vacuo*. Solvent ratios are given in v/v %.

Preparation of (α-Carboethoxyethylidene)-triphenylphosphorane (13) from (Carboethoxymethylene)-triphenylphosphorane (12)——CH_3I (0.88 g) was added dropwise to a stirred solution of **12** (1.90 g) in dry AcOEt (16 ml) under an N_2 atmosphere and the mixture was refluxed for 1.5 h. After concentration of the mixture *in vacuo*, the solid residue was triturated with H_2O (100 ml) and the insoluble material was filtered off. The filtrate was cooled to 0°C and adjusted after addition of ether (2 ml) to pH 7 with 1 N NaOH. The resulting precipitate was collected by filtration, washed with H_2O, dried *in vacuo*, and recrystallized from AcOEt to give **13** (750 mg) as pale yellow needles, mp 159—160°C. IR ν_{max}^{KBr} cm^{-1}: 2940, 1610, 1355, 1295 and 1180. ^{1}H NMR δ: 0.72 (t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 1.52 (s, $\phi_3\overset{+}{P}=\underset{\downarrow}{C}-C\underline{H}_3\times 1/2$), 1.76 (s, $\phi_3\overset{+}{P}-\underset{\downarrow}{C}-C\underline{H}_3\times 1/2$), 3.84 (q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$) and 7.30—7.89 (m, aromatic protons). *Anal.* Calcd for $C_{23}H_{23}O_2P$: C, 76.23; H, 6.40; P, 8.55. Found: C, 76.19; H, 6.31; P, 8.58. Treatment of **12** (1.08 g) with $^{13}CH_3I$ (0.50 g) in the same way as above gave (α-carboethoxy[*methyl*-^{13}C]ethylidene)-triphenylphosphorane (**13**) (375 mg). ^{1}H NMR δ: 1.52 (d, $^1J_{H,C}$=128.5 Hz. $\phi_3P=C-{}^{13}C\underline{H}_3\times 1/2$) and 1.76 (d, $^1J_{H,C}$=128.5 Hz, $\phi_3\overset{+}{P}-\underset{\downarrow}{C}-{}^{13}C\underline{H}_3\times 1/2$).

Preparation of (*E*)-6-Acetoxy-4-methyl-4-hexenal (14) from Geranyl Acetate (15)——A solution of **15** (1.00 g) in dry CH_2Cl_2 (43 ml) containing pyridine (0.41 ml) was cooled to −78°C and treated with a stream of ozonized oxygen until **15** became undetectable on TLC. After the addition of Zn dust (2.62 g) and AcOH (10.5 ml), the reaction mixture was stirred for 2 h at room temperature, then the solid material was filtered off and washed with *n*-hexane. The combined filtrate and washings were shaken successively with 10% $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to vacuum distillation to give **14** (360 mg) as a colorless oil, bp 125°C (4.0 mmHg). IR ν_{max}^{neat} cm^{-1}: 2880, 2690, 1725, 1715 and 1360. ^{1}H NMR δ: 1.74 (d, J=1.0 Hz, 4-CH_3), 2.05 (s, $-OCOCH_3$), 2.35—2.63 (m, 2-H_2, 3-H_2), 4.59 (d, J=7.0 Hz, 6-H_2), 5.40 (m, 5-H) a d 9.79 (t, J=1.0 Hz, 1-H). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.24; H, 8.49.

Preparation of Ethyl (2*E*,6*E*)-8-Acetoxy-2,6-dimethyl-2,6-octadienoate (16) from (α-Carboethoxyethylidene)-triphenylphosphorane (13) and (*E*)-6-Acetoxy-4-methyl-4-hexenal (14)——A solution of **14** (100 mg) in dry CH_2Cl_2 (1.5 ml) was added dropwise to **13** (194 mg) during 10 min under an N_2 atmosphere and the mixture was stirred at room temperature for 15 h. The mixture, on concentration *in vacuo*, gave an oily residue, which was purified by PLC (*n*-hexane–ether 6: 1, 3 developments) to furnish an oily substance. This substance was subjected to vacuum distillation to give **16** (101 mg) as a colorless oil, bp 109—112°C (8.3 mmHg). UV λ_{max}^{MeOH} nm (log ε): 220.5 (4.08). IR ν_{max}^{neat} cm^{-1}: 2920, 1735, 1708, 1368 and 1232. ^{1}H NMR δ: 1.28 (t, J=7.5 Hz, $-COOCH_2C\underline{H}_3$), 1.71 (d, J=1.0 Hz, 6-CH_3), 1.82 (d, J=1.0 Hz, 2-CH_3), 2.03 (s, $-OCOCH_3$), 2.12—2.40 (m, 4-H_2, 5-H_2), 4.19 (q, J=7.5 Hz, $-COOC\underline{H}_2CH_3$), 4.60 (d, J=7.5 Hz, 8-H_2), 5.39 (br t, J=7.5 Hz, 7-H) and 6.71 (br t, J=7.5 Hz, 3-H). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.82; H, 8.98. Reaction of (α-carboethoxy[*methyl*-^{13}C]ethylidene)-triphenylphosphorane (**13**) (111 mg) with **14** (60 mg) in the same way as above gave [2-*methyl*-^{13}C]-**16** (54 mg). ^{1}H NMR δ: 1.82 (dd, $^1J_{H,C}$=127.8 Hz, $^4J_{C\underline{H}_3,H-3}$=1.0 Hz, 2-$^{13}CH_3$).

Reduction of Ethyl (2*E*,6*E*)-8-Acetoxy-2,6-dimethyl-2,6-octadienoate (16)——$AlCl_3$ (88 mg) was added to a stirred suspension of $LiAlH_4$ (74 mg) in dry ether (27 ml), which had been precooled to −15°C, under an N_2 atmosphere and stirring was continued for 30 min. A solution of **16** (97 mg) in dry ether (5 ml) was added dropwise to the above mixture and the whole was stirred at −15—0°C for 1.5 h. After decomposition of the excess reagent with H_2O, the mixture was neutralized with 5% HCl and extracted with ether (5 ml×4). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by PLC (ether) gave an oily substanbce which was subjected to vacuum distillation to give 10-hydroxygeraniol (**9**) (57 mg) as a colorless oil, bp 115°C (1.0 mmHg). IR ν_{max}^{neat} cm^{-1}: 3300, 2910, 1660, 1380 and 835. ^1H NMR δ: 1.64 (m, 4-H_3, 9-H_3), 1.93—2.33 (m, 5-H_2, 6-H_2), 3.15 (br s, −OH×2), 3.96 (s, 10-H_2), 4.12 (d, J=7.0 Hz, 1-H_2) and 5.25—5.49 (m, 2-H, 7-H). *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.43; H, 10.52. Reduction of [2-*methyl*-^{13}C]-**16** (54 mg) with AlH_3, prepared from $LiAlH_4$ and $AlCl_3$, in the same way as above gave [9-^{13}C]-**9** (35 mg). ^1H NMR δ: 1.64 (dd, $^1J_{H-9,C-9}$= 126.0 Hz, $J_{9,7}$=1.0 Hz, 9-H_3) and 3.96 (d, $^3J_{H-10,C-9}$=3.0 Hz, 10-H_2). ^{13}C NMR ($CDCl_3$) δ: 59.18 (t, C_1), 123.94 (d, C_2), 138.61 (s, C_3), 16.15 (q, C_4), 39.04 (t, C_5), 25.71 (t, C_6), 125.23 (d, C_7), 135.97 (s, C_8), 13.74 (q, C_9) and 68.69 (t, C_{10}). High-resolution MS m/z: Calcd for $C_9{}^{13}CH_{18}O_2$ /(M^+) 171.1340. Found: 171.1343.

Preparation of 4-Tetrahydropyranyloxybutanol (17) from 1,4-Butanediol——A solution of 1,4-butanediol (4.50 g), 2,3-dihydropyran (4.62 g) and PPTS (1.25 g) in dry CH_2Cl_2 (30 ml) was stirred at room temperature for 30 min and then the solvent was removed *in vacuo*. The residue was taken up in ether (50 ml) and the ethereal solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting colorless oil (4.55 g) was chromatographed on a silica gel column (25 g) with benzene (100 ml) and benzene–ether (95: 5, 200 ml) as eluents, collecting 15 ml fractions. Fr. 6—15 were combined and concentrated to give **17** (3.95 g) as a colorless oil, bp 98° (1.8 mmHg). IR ν_{max}^{neat} cm^{-1}: 3350, 2900 and 1120. ^1H NMR δ: 1.65 (m, 6H of pyran ring, 2-H_2, 3-H_2), 2.87 (br s, −OH), 3.60 (m, 2H of pyran ring, 1-H_2, 4-H_2) and 4.57 (m, −O−CH−O−). *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.30; H, 10.38.

Oxidation of 4-Tetrahydropyranyloxybutanol (17)——PDC (5.88 g) was added to a solution of **17** (1.81 g) in dry CH_2Cl_2 (10 ml) and the whole was stirred at room temperature for 4 h. On dilution of the mixture with ether (30 ml), the resulting precipitate was filtered off and washed with ether. After concentration of the combined filtrate and washings, the resulting pale brown oil (2.16 g) was chromatographed on a silica gel column (10 g) with benzene as the eluent, collecting 15 ml fractions. Fr. 2—6 were combined and concentrated *in vacuo*. The residue (1.72 g) was subjected to vacuum distillation to give 4-tetrahydropyranyloxybutanal (**18**) (1.51 g) as a colorless oil, bp 78° (1.8 mmHg). IR ν_{max}^{neat} cm^{-1}: 2900, 2690, 1710 and 1115. ^1H NMR δ: 2.54 (dt, $J_{2,1}$=1.5 Hz, $J_{2,3}$=6.5 Hz, 2-H_2), 4.55 (m, −O−CH−O−) and 9.73 (t, J=1.5 Hz,1-H). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.91; H, 9.53.

Preparation of Ethyl (*E*)-2-Methyl-6-tetrahydropyranyloxy-2-hexenoate (19) from 4-Tetrahydropyranyloxybutanal (18) and (α-Carboethoxyethylidene)-triphenylphosphorane (13)——A solution of **18** (622 mg) in dry CH_2Cl_2 (8 ml) was added dropwise to **13** (1.29 g) under an N_2 atmosphere and the mixture was stirred at room temperature for 15 h. After concentration of the mixture *in vacuo*, the residue was purified by PLC (*n*-hexane–ether 6: 1, 3 developments) followed by vacuum distillation to give **19** (703 mg) as a colorless oil, bp 94°C (0.9 mmHg). UV λ_{max}^{MeOH} nm (log ε): 227.0 (3.84). IR ν_{max}^{neat} cm^{-1}: 2910, 1700, 1365, 1260 and 1135. ^1H NMR δ: 1.28 (t, J=7.0 Hz, −$COOCH_2C\underline{H}_3$), 1.84 (br s, 2-CH_3), 4.17 (q, J=7.0 Hz, −$COOC\underline{H}_2CH_3$), 4.54 (m, −O−CH−O−) and 6.76 (br t, J=7.5 Hz, 3-H). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.35; H, 9.55.

Preparation of Ethyl (*E*)-6-Hydroxyl-2-methy-2-hexenoate (20) from Ethyl (*E*)-2-Methyl-6-tetrahydropyranyloxy-2-hexenoate (19)——PPTS (105 mg) was added to a solution of **19** (1.07 g) in EtOH (25 ml) and the whole was stirred at 50°C for 7.5 h. On concentration *in vacuo*, the solution gave an oily residue, which was purified by PLC (ether) followed by vacuum distillation to furnish **20** (803 mg) as a colorless oil, bp 91—95°C (1.0 mmHg). UV λ_{max}^{MeOH} nm (log ε): 218.0 (4.09). IR ν_{max}^{neat} cm^{-1}: 3350, 2910, 1700, 1640, 1365 and 1260. ^1H NMR δ: 1.28 (t, J=7.0 Hz, −$COOCH_2C\underline{H}_3$), 1.84 (br s, 2-CH_3), 2.47 (br s, −OH), 3.64 (t, J= 6.0 Hz, 6-H_2), 4.17 (q, J=7.0 Hz, −$COOC\underline{H}_2CH_3$) and 6.75 (br t, J=7.5 Hz, 3-H). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.49; H, 9.19.

Oxidation of Ethyl (*E*)-6-Hydroxy-2-methyl-2-hexenoate (20)——PDC (1.50 g) was added to a solution of **20** (456 mg) in dry CH_2Cl_2 (3.7 ml) and the whole was stirred at room temperature for 4 h. On dilution of the mixture with ether (20 ml), the resulting precipitate was filtered off and washed with ether. On concentration, the combined filtrate and washings gave a pale brown oil (392 mg), which was purified by PLC (*n*-hexane–ether 1: 1) followed by vacuum distillation to give ethyl (*E*)-2-methyl-6-oxo-2-hexenoate (**21**) (284 mg) as a colorless oil, bp 86—89°C (3.6 mmHg). UV λ_{max}^{MeOH} nm (log ε): 217.0 (4.15). IR ν_{max}^{neat} cm^{-1}: 2900, 2690, 1695, 1360 and 1260. ^1H NMR δ: 1.28 (t, J=7.0 Hz, −$COOCH_2C\underline{H}_3$), 1.87 (br s, 2-CH_3), 4.18 (q, J=7.0 Hz, −$COOC\underline{H}_2CH_3$), 6.68 (br t, J=7.0 Hz, 3-H) and 9.77 (t, J=1.0 Hz, 6-H). High-resolution MS m/z: Calcd for $C_9H_{14}O_3$ (M^+) 170.0943. Found: 170.0962.

Preparation of Ethyl (*E*)-6-Hydroxy-2-methyl-2-heptenoate (22) from Ethyl (*E*)-2-Methyl-6-oxo-2-hexenoate (21)——A solution of **21** (362 mg) in dry ether (4 ml) was added dropwise at −20°C during 10 min to a stirred solution of CH_3MgI, prepared from Mg (72 mg) and CH_3I (514 mg) in dry ether (10 ml) in the usual manner, and the whole was stirred at −20°C for 1.5 h. The mixture was poured into ice-water, neu-

tralized with 1 N HCl, saturated with NaCl and then extracted with ether (10 ml×4). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue (354 mg) by PLC (*n*-hexane–ether 1: 2) gave an oily residue, which afforded on vacuum distillation a colorless oil, **22** (247 mg), bp 97—99°C (1.2 mmHg). UV λ_{max}^{MeOH} nm (log ε): 217.5 (4.13). IR ν_{max}^{neat} cm^{-1}: 3350, 2930, 1695, 1640, 1360 and 1265. ^1H NMR δ: 1.21 (d, J=6.5 Hz, 7-H_3), 1.27 (t, J=7.0 Hz, $-COOCH_2-C\underline{H}_3$), 1.83 (br s, 2-$CH_3$), 3.79 (sextet, J=6.5 Hz, 6-H), 4.18 (q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$) and 6.75 (br t, J=7.0 Hz, 3-H). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.74; H, 10.04. Treatment of **21** (595 mg) with $^{13}CH_3MgI$, prepared from Mg (119 mg) and $^{13}CH_3I$ (845 mg), in the same way as above gave [7-^{13}C]-**22** (516 mg). ^1H NMR δ: 1.21 (dd, $^1J_{H-7,C-7}$=125.5 Hz, $J_{7,6}$=6.5 Hz, 7-H_3).

Oxidation of Ethyl (*E*)-6-Hydroxy-2-methyl-2-heptenoate (22)——Jones reagent (0.8 ml) was added dropwise to a solution of **22** (255 mg) in acetone (8 ml) under ice-cooling. The mixture was stirred at 0°C for 30 min and then poured into ice-water and extracted with ether (10 ml×4). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue (230 mg) by PLC (*n*-hexane–ether 1: 1) followed by vacuum distillation gave ethyl (*E*)-2-methyl-6-oxo-2-heptenoate (**23**) (198 mg) as a colorless oil, bp 102—105°C (1.8 mmHg). UV λ_{max}^{MeOH} nm (log ε): 217.5 (4.05). IR (ν_{max}^{neat} cm^{-1}: 2900, 1700, 1640 and 1360. ^1H NMR δ: 1.28 (t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 1.85 (br s, 2-CH_3), 2.14 (s, 7-H_3), 4.17 (q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$) and 6.65 (br t, J=7.0 Hz, 3-H). *Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.06; H, 8.90. Jones oxidation of [7-^{13}C]-**22** (516 mg) in the same way as above gave [7-^{13}C]-**23** (428 mg). ^1H NMR δ: 2.14 (d, $^1J_{H-7,\ C-7}$=125.5 Hz, 7-H_3).

Preparation of Diethyl Ethoxycarbonylmethylphosphonate (24) from Diethyl Phosphite——Diethyl carbonylmethyl phosphonate[13] (300 mg) prepared from diethyl phosphite, CH_3I and dry ice was dissolved in ether (5 ml) and treated with ethereal diazoethane under ice-cooling. The reaction mixture, which retained a light yellow color, was allowed to stand at 0°C for 30 min and then evaporated to dryness *in vacuo*. The residue (341 mg) was subjected to vacuum distillation to give **24** (306 mg) as a colorless oil, bp 105—108°C (1.7 mmHg). IR ν_{max}^{neat} cm^{-1}: 2910, 1730, 1270 and 1020. ^1H NMR δ: 1.27 (t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 1.33 (t, J=7.0 Hz, $-OCH_2C\underline{H}_3\times2$), 2.93 (d, $^2J_{H,P}$=21.5 Hz, ϕP(O)–$C\underline{H}_2$–), 4.06 and 4.21 (each q, J=7.0 Hz, $-OC\underline{H}_2CH_3$) and 4.16 (q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$). *Anal.* Calcd for $C_8H_{17}O_5P$: C, 42.86; H, 7.64; P, 13.82. Found: C, 42.81; H, 7.90; P, 14.10. Treatment of diethyl carbonyl[^{13}C]methylphosphonate (700 mg), prepared from diethyl phosphite, $^{13}CH_3I$ and dry ice, with diazoethane in the same way as above gave diethyl ethoxycarbonyl[^{13}C]methylphosphonate (**24**) (844 mg). ^1H NMR δ: 2.93 (dd, $^1J_{H,C}$=129.0 Hz, $^2J_{H,P}$=21.5 Hz, ϕP(O)–$^{13}C\underline{H}_2$–).

Preparation of Diethyl 2-Methyl-1,5-heptadiene-1,6-dicarboxylate (25) from Ethyl (*E*)-2-Methyl-6-oxo-2-heptenoate (23) and Diethyl Ethoxycarbonylmethylphosphonate (24)——Compound **24** (61 mg) was added dropwise to a stirred suspension of NaH (13 mg, 50% dispersion of NaH in mineral oil) in dry THF (1 ml) during 15 min at room temperature under an N_2 atmosphere. Stirring was continued for 1 h, then a solution of **23** (50 mg) in dry THF (1 ml) was added dropwise to the mixture during half an h at room temperature. The whole was stirred at room temperature for a further half h and then at 60—65°C for 3 h. The mixture was poured into ice-water and extracted with $CHCl_3$ (5 ml×4). The combined $CHCl_3$ extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (122 mg) was purified by PLC (*n*-hexane–ether 1: 1) to afford an oily substance (37 mg), which, on vacuum distillation, gave **25** (32 mg) as a colorless oil, bp 98—101°C (2.7 mmHg). UV λ_{max}^{MeOH} nm (log ε): 220.0 (4.37). IR ν_{max}^{neat} cm^{-1}: 2950, 1705, 1645, 1365, 1270 and 835. ^1H NMR δ: 1.27 (t, J=7.0 Hz, $-COOCH_2C\underline{H}_3\times2$), 1.85 (br s, 7-$H_3$), 1.93 (d, $^4J_{C\underline{H}_3,H-1}$=1.2 Hz, 2-$CH_3\times1/5$), 2.17 (d, $^4J_{C\underline{H}_3,H-1}$=1.2 Hz, 2-$CH_3\times4/5$), 4.14 and 4.17 (each q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$), 5.66 (br s, 1-H) and 6.66 (br t, J=7.0 Hz, 5-H). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.34; H, 8.94. Treatment of [7-^{13}C]-**23** (428 mg) with **24** (483 mg) in the same way as above gave [2-*methyl*-^{13}C]-**25** (365 mg). ^1H NMR δ: 1.93 (dd, $^1J_{H,C}$=127.0 Hz, $^4J_{C\underline{H}_3,H-1}$=1.2 Hz, 2-$^{13}CH_3\times1/5$), 2.17 (dd, $^1J_{H,C}$=127.0 Hz, $^4J_{C\underline{H}_3,H-1}$=1.2 Hz, 2-$^{13}CH_3\times4/5$) and 5.66 (br d, $^3J_{H-1,C}$=8.0 Hz, 1-H).

Reduction of Diethyl 2-Methyl-1,5-heptadiene-1,6-dicarboxylate (25)——A solution of **25** (37 mg) in dry ether (2 ml) was added dropwise to a stirred slurry of AlH_3, prepared from $LiAlH_4$ (33 mg) and $AlCl_3$ (40 mg) in dry ether (15 ml), during 10 min at −15°C under an N_2 atmosphere. The mixture was stirred at −15—0°C for 1.5 h, then the excess reagent was decomposed with H_2O. The mixture was neutralized with 5% HCl and extracted with ether (5 ml×4). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue (28 mg) by PLC (ether) followed by vacuum distillation gave a colorless oily mixture (20 mg) of 10-hydroxygeraniol (**9**) and 10-hydroxynerol (**26**) (4: 1), bp 126—128°C (1.8 mmHg). IR ν_{max}^{neat} cm^{-1}: 3350 and 2900. ^1H NMR δ: 1.66 (br s, 4-$H_3\times4/5$, 9-H_3), 1.77 (br s, 4-$H_3\times1/5$), 2.33 (br s, -OH×2), 3.96 (br s, 10-H_2), 4.11 (d, J=7.0 Hz, 1-H_2) and 6.37 (m, 2-H, 7-H). *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.79; H, 10.89. Reduction of [2-*methyl*-^{13}C]-**25** (365 mg) with AlH_3 in the same way as above gave a mixture (242 mg) of [4-^{13}C]-**9** and [4-^{13}C]-**26** (4: 1). ^1H NMR δ: 1.66 (d, $^1J_{H-4,C-4}$=125.5 Hz, 4-$H_3\times4/5$) and 1.77 (d, $^1J_{H-4,C-4}$=125.5 Hz, 4-$H_3\times1/5$). ^{13}C NMR ($CDCl_3$) δ: 58.97 (t, C_1), 123.96 (d, C_2), 124.54 (d, C_2 of **26**), 138.48 (s, C_3), 16.05 (q, C_4), 23.17 (q, C_4 of **26**), 38.98 (t, C_5), 31.28 (t, C_5 of **26**), 25.50 (t, C_6), 124.93 (d, C_7), 134.91 (s, C_8), 13.65 (q, C_9) and 68.34 (t, C_{10}). High-resolution MS m/z: Calcd for $C_9{}^{13}CH_{18}O_2(M^+)$ 171.1340. Found: 171.1330.

Preparation of 2-Acetoxy-5-iodopentane (29) from α-Acetyl-γ-butyrolactone (28)——A solution of 5-

iodopentan-2-one (**27**)[15] (1.74 g), prepared by decarboxyhalogenation of **28** using conc. HI, in MeOH (8 ml) was added to a stirred solution of $NaBH_4$ (550 mg) in MeOH (20 ml) during 10 min under ice-cooling. The mixture was stirred at 0°C for 20 min and the excess reagent was decomposed with acetone. The mixture was neutralized with methanolic 5% AcOH and concentrated *in vacuo*. The residue was dissolved in ether (50 ml), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Acetylation of the residue (1.57 g) with 3 ml each of Ac_2O and pyridine in the usual manner gave a pale yellow oily product (1.82 g), which was subjected to vacuum distillation to afford **29** (1.65 g) as a colorless oil, bp 92°C (6.0 mmHg). IR ν_{max}^{neat} cm^{-1}: 2910, 1720 and 1365. ^1H NMR δ: 1.24 (d, J=6.0 Hz, 1-H_3), 1.45—2.15 (m, 3-H_2, 4-H_2), 2.03 (s, $-OCOCH_3$), 3.20 (t, J=6.5 Hz, 5-H_2) and 4.91 (sextet, J=6.0 Hz, 2-H). *Anal.* Calcd fo $C_7H_{13}IO_2$: C, 32.83; H, 5.12; I, 49.56. Found: C, 32.62; H, 5.27; I, 49.65.

Preparation of Bis(tetrahydropyranyloxy)acetone (31) from Dihydroxyacetone (32)——2,3-Dihydropyran (1.71 g) and PPTS (340 mg) were added to a suspension of **32** (500 mg) in dry CH_2Cl_2 (10 ml) and the whole was stirred at 30—35°C for 3.5 h. After concentration of the mixture *in vacuo*, the residue was taken up in ether (20 ml) and the ethereal solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The colorless syrupy residue (1.53 g) was recrystallized from *n*-hexane–ether to give **31** (852 mg) as colorless needles, mp 49—50°C. IR ν_{max}^{neat} cm^{-1}: 1710 and 1115. ^1H NMR δ: 1.70 (m, 12H of pyran rings), 3.70 (m, 4H of pyran rings), 4.38 (d, J=1.0 Hz, 1-H_2, 3-H_2) and 4.64 (br t, J=2.5 Hz, $-O-\underset{|}{C}H-O-\times 2$). *Anal.* Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.21; H, 8.46.

Wittig Reaction of Bis(tetrahydropyranyloxy)acetone (31) with (4-Acetoxypentane)-triphenylphosphonium Iodide (30) derived from 2-Acetoxy-5-iodopentane (29)——Triphenylphosphine (419 mg) was added to a solution of **29** (410 mg) in dry benzene (5 ml) and the mixture was stirred at 70—80°C for 40 h under an N_2 atmosphere. After removal of the solvent by decantation, the residual pale yellow syrup (**30**) (788 mg) was dissolved in dry THF (4 ml). This solution was cooled to −20°C, then a solution of *n*-BuLi in hexane (2.85 ml, 1.6 M solution) was added dropwise during 5 min under an N_2 atmosphere. The mixture was stirred at −15—0°C for 2 h and then at room temperature for 10 min. This mixture was cooled again to −20°C, and a solution of **31** (392 mg) in dry THF (2 ml) was added dropwise during 5 min. The whole solution was stirred at −20°C for a further half h. Then it was stirred at room temperature for 1 h. Finally it was stirred at 70—80°C for 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$ (8 ml×4). The combined $CHCl_3$ extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the pale brown oily residue (1.12 g) by PLC (ether) gave 6,6-bis(tetrahydropyranyloxymethyl)-5-hexen-2-ol (**33**) (208 mg) as a colorless oil which was not distillable because of its lability. IR ν_{max}^{neat} cm^{-1}: 3350, 2910 and 1115. ^1H NMR δ: 1.17 (d, J=6.0 Hz, 1-H_3), 4.61 (m, $-O-\underset{|}{C}H-O-\times 2$) and 5.67 (br t, J=7.5 Hz, 5-H). *Anal.* Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.68; H, 9.61.

Oxidation of 6,6-Bis(tetrahydropyranyloxymethyl)-5-hexen-2-ol (33)——PDC (337 mg) was added to a solution of **33** (196 mg) in dry CH_2Cl_2 (2 ml) and the whole was stirred at room temperature for 20 h. The mixture was diluted with ether (10 ml) and the resulting precipitate was filtered off and washed with ether. After concentration of the combined filtrate and washings *in vacuo*, the residual pale brown oil (194 mg) was purified by PLC (ether) to furnish 6,6-bis(tetrahydropyranyloxymethyl)-5-hexen-2-one (**34**) (152 mg) as a colorless oil which was not distillable because of its lability. IR ν_{max}^{neat} cm^{-1}: 2920, 1715 and 1120. ^1H NMR δ: 2.12 (s, 1-H_3), 4.59 (m, $-O-\underset{|}{C}H-O-\times 2$) and 5.62 (br t, J=6.5 Hz, 5-H). *Anal.* Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.09; H, 9.13.

Wittig Reaction of 6,6-Bis(tetrahydropyranyloxymethyl)-5-hexen-2-one (34) with Diethyl Ethoxycarbonylmethylphosphonate (24)——Compound **24** (224 mg) was added dropwise to a suspension of NaH (48 mg, 50% dispersion of NaH in mineral oil) in dry THF (3 ml) during 15 min at room temperature under an N_2 atmosphere. The mixture was stirred for 1 h, then a solution of **34** (326 mg) in dry THF (1 ml) was added dropwise to the mixture during 30 min, and the whole was stirred at room temperature for a further half h and then at 60—65°C for 3 h. The mixture was poured into ice-water and extracted with $CHCl_3$ (5 ml×4). The combined $CHCl_3$ extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. PLC (*n*-hexane–ether 1: 1) of the residue (421 mg) gave along with starting materials, **24** (*Rf* 0.03, 74 mg), **34** (*Rf* 0.17, 68 mg), a colorless oily mixture (*Rf* 0.42, 271 mg) of ethyl 9,10-bis(tetrahydropyranyloxy)geranate (**35a**) and the corresponding nerate (**35b**) (4: 1) which was not distillable because of its lability. UV λ_{max}^{MeOH} nm (log ε): 219.5 (4.17). IR ν_{max}^{neat} cm^{-1}: 2920, 1705, 1640 and 1140. ^1H NMR δ: 1.26 (t, J=7.0 Hz, $-COO-CH_2\underline{CH_3}$), 1.87 (d, $J_{4,2}$=1.2 Hz, 4-$H_3\times 1/5$), 2.15 (d, $J_{4,2}$=1.2 Hz, 4-$H_3\times 4/5$), 4.60 (m, $-O-\underset{|}{C}H-O-\times 2$) and 5.64 (m, 2-H, 7-H). *Anal.* Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.42; H, 9.20. Treatment of ^{13}C-labeled **24** (562 mg) with **34** (726 mg) in the same way as above gave a mixture (532 mg) of [2-^{13}C]-**35a** and [2-^{13}C]-**35b** (4: 1). ^1H NMR δ: 1.87 (dd, $^3J_{H-4,C-2}$=5.0 Hz, $J_{4,2}$=1.2 Hz, 4-$H_3\times 1/5$), 2.15 (dd, $^3J_{H-4,C-2}$=5.0 Hz, $J_{4,2}$=1.2 Hz, 4-$H_3\times 4/5$) and 5.64 (br d, $^1J_{H-2,C-2}$=159.0 Hz, 2-H).

Reduction of the Mixture of Ethyl 9,10-Bis(tetrahydropyranyloxy)geranate (35a) and the Corresponding Nerate (35b)——A solution of the mixture (**35a** and **35b**) (178 mg) in dry ether (5 ml) was added dropwise to a stirred slurry of AlH_3, prepared from $LiAlH_4$ (78 mg) and $AlCl_3$ (98 mg) in dry ether (30 ml), during 10 min at −15°C under an N_2 atmosphere. After further stirring at −15—0°C for 1.5 h, the excess reagent was decomposed with H_2O and the mixture was extracted with ether (10 ml×4). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (124 mg) was

purified by PLC (ether) to afford a colorless mixture (122 mg) of 9,10-bis(tetrahydropyranyloxy)geraniol (**36a**) and the corresponding nerol derivative (**36b**) (4: 1) which was not distillable because of its lability. IR ν_{max}^{neat} cm^{-1}: 3400, 2925, 1110 and 1075. ^1H NMR δ: 1.65 (br s, 4-H_3), 2.03 (br s, –OH), 4.60 (m, –O–CH–O–×2), 5.37 (br t, J=7.0 Hz, 2-H) and 5.62 (br t, J=7.0 Hz, 7-H) *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found: C, 67.47; H, 9.43. Reduction of a mixture (532 mg) of [2-^{13}C]-**35a** and [2-^{13}C]-**35b** (4: 1) with AlH_3 in the same way as above gave a mixture (420 mg) of [2-^{13}C]-**36a** and [2-^{13}C]-**36b** (4: 1). ^1H NMR δ: 5.37 (dt, $^1J_{H-2,C-2}$=149.5 Hz, $J_{2,1}$=7.0 Hz, 2-H).

Removal of the Tetrahydropyranyl Group from the Mixture of 9,10-Bis(tetrahydropyranyloxy)geraniol (36a) and the Corresponding Nerol Derivative (36b)——PPTS (7.8 mg) was added to a solution of the mixture (**36a**) and **36b**) (111 mg) in EtOH (2.5 ml) and the whole was stirred at 50°C for 9 h. After removal of the solvent *in vacuo*, the residue was purified by PLC (ether) to provide a colorless oil (43 mg) consisting of 9,10-dihydroxygeraniol (**10**) and 9,10-dihydroxynerol (**37**) (4: 1). This oil was not distillable. IR ν_{max}^{neat} cm^{-1}: 3300, 2900, 1665 and 1005. ^1H NMR δ: 1.68 (br s, 4-H_3×4/5), 1.75 (br s, 4-H_3×1/5), 1.79 (br s, –OH×3), 4.10 (br d, J=7.0 Hz, 1-H_2), 4.16 (br s, 10-H_2), 4.21 (br s, 9-H_2), 5 36 (br t, J=7.0 Hz, 2-H) and 5.46 (br t, J=7.0 Hz, 7-H). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.23; H, 9.93. Treatment of a mixture (420 mg) of [2-^{13}C]-**36a** and [2-^{13}C]-**36b** (4: 1) with PPTS in the same way as above gave a mixture (195 mg) of [2-^{13}C]-**10** and [2-^{13}C]-**37** (4: 1). ^1H NMR δ: 1.68 (br d, $^3J_{H-4,C-2}$=5.0 Hz, 4-H_3×4/5), 1.75 (br d, $^3J_{H-4,C-2}$=5.0 Hz, 4-H_3×1/5) and 5.36 (dt, $^1J_{H-2,C-2}$=152.0 Hz, $J_{2,1}$=7.0 Hz, 2-H). ^{13}C NMR (CD_3OD) δ: 58.26 (t, C_1), 125.03 (d, C_2), 125.88 (d, C_2 of **37**), 137.85 (s, C_3), 16.20 (q, C_4), 23.56 (q, C_4 of **37**), 39.93 (t, C_5), 32.69 (t, C_5 of **37**), 26.45 (t, C_6), 129.37 (d, C_7), 139.21 (s, C_8), 58.70 (t, C_9) and 65.38 (t, C_{10}). High-resolution MS m/z: Calcd for $C_9{}^{13}CH_{18}O_3$ (M^+) 187.1289. Found: 187.1307.

Preparation of (*R*)-(+)-Citronellyl Acetate ((*R*)-(+)-40) from (*R*)-(+)-Pulegone (39)——(*R*)-(+)-Citronellol ((*R*)-(+)-**38**)[16] (0.99 g) derived from **39** was acetylated in the usual manner to afford (*R*)-(+)-**40** (1.18 g) as a colorless oil, bp 64—69°C (0.8 mmHg). $[\alpha]_D^{20}$ +3.51° (c=13.16, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2900, 1735 and 1360. ^1H NMR δ: 0.92 (d, J=6.0 Hz, 4-H_3), 1.62 (br s, 9-H_3), 1.69 (br s, 10-H_3), 2.03 (s, –$OCOCH_3$), 4.12 (t, J=6.5 Hz, 1-H_2) and 5.11 (br t, J=7.0 Hz, 7-H). *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.56; H, 11.41.

Preparation of (*R*)-(+)-6-Acetoxy-4-methylhexanal ((*R*)-(+)-41) from (*R*)-(+)-Citronellyl Acetate ((*R*)-(+)-40)——A solution of (*R*)-(+)-**40** (991 mg) in dry CH_2Cl_2 (40 ml) was cooled to −78°C and treated with a stream of ozonized oxygen until the mixture showed a persistent pale blue color. After concentration of the mixture at room temperature *in vacuo*, the residue was dissolved in a mixture of EtOH (25 ml), H_2O (2.5 ml) and AcOH (0.8 ml). Zn dust (500 mg) was added in small portions to the well-stirred mixture during the next 50 min, then the whole was stirred for an additional hour at room temperature. The insoluble material was filtered off and the filtrate was concentrated *in vacuo* to afford a residue, which was suspended in H_2O and extracted with ether (5 ml×4). The combined ethereal extracts were washed successively with 10% $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Vacuum distillation of the oily residue (658 mg) gave (*R*)-(+)-**41** (474 mg) as a colorless oil, bp 82—85°C (0.7 mmHg). $[\alpha]_D^{20}$ +2.34° (c= 6.42, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2910, 2700, 1730 and 1365. ^1H NMR δ: 0.94 (d, J=5.5 Hz, 4-CH_3), 2.03 (s, –$OCOCH_3$), 4.13 (t, J=6.5 Hz, 6-H_2) and 9.79 (t, J=1.8 Hz, 1-H). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.49; H, 9.43.

Wittig Reaction of (*R*)-(+)-6-Acetoxy-4-methylhexanal ((*R*)-(+)-41) with (α-Carboethoxyethylidene)-triphenylphosphorane (13)——A solution of (*R*)-(+)-**41** (353 mg) in dry CH_2Cl_2 (3.0 ml) was added to **13** (743 mg) during 5 min under an N_2 atmosphere and the whole was stirred at room temperature for 15 h. After concentration of the mixture *in vacuo*, the residue was purified by PLC (*n*-hexane–ether 6: 1, 2 developments) followed by vacuum distillation to give ethyl (*E*)-(*R*)-(+)-8-acetoxy-2,6-dimethyl-2-octenoate ((*R*)-(+)-**42**) (443 mg) as a colorless oil, bp 119—122°C (3.7 mmHg). $[\alpha]_D^{20}$ +5.37° (c=4.24, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 217.5 (4.11). IR ν_{max}^{neat} cm^{-1}: 2910, 1735, 1705 and 1365. ^1H NMR δ: 0.95 (d, J=5.5 Hz, 6-CH_3), 1.29 (t, J=7.3 Hz, –$COOCH_2\underline{CH}_3$), 1.83 (br s, 2-CH_3), 2.03 (s, –$OCOCH_3$), 4.19 (q, J=7.3 Hz, –$COO\underline{CH}_2CH_3$) and 6.75 (br t, J=7.0 Hz, 3-H). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.52; H, 9.49. Treatment of ^{13}C-labeled **13** (311 mg) with (*R*)-(+)-**41** (148 mg) in the same way as above gave (*R*)-(+)-[2-*methyl*-^{13}C]-**42** (172 mg). ^1H NMR δ: 1.83 (br d, $^1J_{H,C}$=128.0 Hz, 2-$^{13}CH_3$) and 6.75 (dt, $^3J_{H-3,C}$=7.5 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Reduction of Ethyl (*E*)-(*R*)-(+)-8-Acetoxy-2,6-dimethyl-2-octenoate ((*R*)-(+)-42)——A solution of (*R*)-(+)-**42** (184 mg) in dry ether (10 ml) was added dropwise to a stirred slurry of AlH_3, prepared from $LiAlH_4$ (163 mg) and $AlCl_3$ (195 mg) in dry ether (30 ml), during 10 min at −15°C under an N_2 atmosphere. The whole was stirred at −15—0°C for a further 1.5 h and the excess reagent was decomposed with H_2O. The mixture was extracted with ether (10 ml×4) and the ethereal layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by PLC (ether) followed by vaccum distillation gave (*R*)-(+)-10-hydroxycitronellol ((*R*)-(+)-**8**) (104 mg) as a colorless oil, bp 116—118°C (2.3 mmHg). $[\alpha]_D^{20}$ +3.70° (c=5.48, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 3270, 2900 and 1375. ^1H NMR δ: 0.90 (d, J=5.5 Hz, 4-H_3), 1.64 (br s, 9-H_3), 2.23 (br s, –OH×2), 3.63 (t, J=6.5 Hz, 1-H_2), 3.94 (br s, 10-H_2) and 5.37 (br t, J=7.0 Hz, 7-H). *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.54; H, 11.46. Reduction of (*R*)-(+)-[2-*methyl*-^{13}C]-**42** (172 mg) with AlH_3 in the same way as above gave (*R*)-(+)-[9-^{13}C]-**8** (110 mg). ^1H NMR

δ: 1.64 (br d, $^1J_{H-9,C-9}=125.5$ Hz, 9-H_3) and 5.37 (dt, $^3J_{H-7,C-9}=7.5$ Hz, $J_{7,6}=7.0$ Hz, 7-H). ^{13}C NMR ($CDCl_3$) δ: 60.84 (t, C_1), 39.76 (t, C_2), 29.07 (d, C_3), 19.55 (q, C_4), 36.75 (t, C_5), 25.01 (t, C_6), 126.12 (d, C_7), 134.50 (s, C_8), 13.62 (q, C_9) and 68.73 (t, C_{10}). High-resolution MS *m/z*: Calcd for $C_9{}^{13}CH_{20}O_2$ (M^+) 173.1497. Found: 173.1493.

Preparation of (*S*)-(−)-Citronellol ((*S*)-(−)-38) from (+)-α-Pinene (44)——2-Methyl-2-butene (924 mg) was added to a stirred slurry of $NaBH_4$ (188 mg) in dry THF (4 ml) at room temperature under an N_2 atmosphere. The mixture was cooled in an ice-bath and BF_3 etherate (1.73 ml of about 47% solution) was added dropwise to the well-stirred reaction mixture during 30 min. After stirring for an additional 1.5 h at 0—5°C, (*S*)-(−)-3,7-dimethyl-1,6-octadiene (**43**)[17] (828 mg) derived from **44** was added to this mixture during 5 min and the whole was stirred at room temperature for 3 h. Then 3 N NaOH (4 ml) and H_2O_2 (30% solution, 3 ml) were added successively to the mixture at a temperature below 50°C and the whole was stirred for 1.5 h at room temperature. The mixture was extracted with ether (10 ml×4) and the combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (1.20 g) was purified by PLC (ether) to afford an oily substance which, on vacuum distillation, gave a colorless oil, (*S*)-(−)-**38** (761 mg), bp 73—78°C (0.4 mmHg). $[\alpha]_D^{15}$ −4.09° (*c*=5.63, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 3300, 2900, 1375 and 1055. ^1H NMR δ: 0.90 (d, J=5.8 Hz, 4-H_3), 1.63 (br s, 9-H_3), 1.68 (br s, 10-H_3), 2.60 (br s, –OH), 3.65 (t, J=6.5 Hz, 1-H_2) and 5.12 (br t, J=7.0 Hz, 7-H). *Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.75; H, 13.19.

Acetylation of (*S*)-(−)-Citronellol ((*S*)-(−)-38)——(*S*)-(−)-**38** (2.00 g) was acetylated with 2 ml each of Ac_2O and pyridine in the usual manner to give (*S*)-(−)-citronellyl acetate ((*S*)-(−)-**40**) (2.04 g) as a colorless oil, bp 90—92°C (3.6 mmHg). $[\alpha]_D^{20}$ −3.43° (*c*=10.30, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.71; H, 11.01.

Preparation of (*S*)-(−)-6-Acetoxy-4-methylhexanal ((*S*)-(−)-41) from (*S*)-(−)-Citronellyl Acetate ((*S*)-(−)-40)——Ozonolysis of (*S*)-(−)-**40** (1.50 g) by the same treatment as in the case of (*R*)-(+)-**40** gave (*S*)-(−)-**41** (737 mg) as a colorless oil, bp 93—95°C (3.7 mmHg). $[\alpha]_D^{20}$ −2.19° (*c*=9.12, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. High-resolution MS *m/z*: Calcd for $C_9H_{16}O_3$ (M^+) 172.1099. Found: 172.1118.

Wittig Reaction of (*S*)-(−)-6-Acetoxy-4-methylhexanal ((*S*)-(−)-41) with (α-Carboethoxyethylidene)-triphenylphosphorane (13)——Treatment of (*S*)-(−)-**41** (95 mg) with **13** (203 mg) in the same manner as in the case of the preparation of (*R*)-(+)-**42** furnished ethyl (*E*)-(*S*)-(−)-8-acetoxy-2,6-dimethyl-2-octenoate ((*S*)-(−)-**42**) (92 mg) as a colorless oil, bp 109—112°C (3.0 mmHg). $[\alpha]_D^{20}$ −4.85° (*c*=6.80, $CHCl_3$). UV, IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.32; H, 9.42. Treatment of (*S*)-(−)-**41** (210 mg) with ^{13}C-labeled **13** (447 mg) in the same way as above gave (*S*)-(−)-[2-*methyl*-^{13}C]-**42** (273 mg).

Reduction of Ethyl (*E*)-(*S*)-(−)-8-Acetoxy-2,6-dimethyl-2-octenoate ((*S*)-(−)-42)——(*S*)-(−)-**42** (91 mg) was reduced with AlH_3, prepared from $LiAlH_4$ (82 mg) and $AlCl_3$ (97 mg), to afford (*S*)-(−)-10-hydroxycitronellol ((*S*)-(−)-**8**) (52 mg) as a colorless oil, bp 104—107°C (0.6 mmHg). $[\alpha]_D^{20}$ −4.39° (*c*=2.73, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.76; H, 11.97. Reduction of (*S*)-(−)-[2-*methyl*-^{13}C]-**42** (273 mg) with AlH_3 in the same way as above gave (*S*)-(−)-[9-^{13}C]-**8** (182 mg). High-resolution MS *m/z*: Calcd for $C_9{}^{13}CH_{20}O_2$(M^+) 173.1497. Found: 173.1502.

Preparation of (*R*)-(+)-6-Acetoxy-4-methylhexanol ((*R*)-(+)-45) from (*R*)-(+)-Citronellyl Acetate ((*R*)-(+)-40)——A solution of (*R*)-(+)-**40** (1.50 g) in dry CH_2Cl_2 (30 ml) was cooled to −78°C and treated with a stream of ozonized oxygen until the solution showed a persistent pale blue color. The resulting solution was added to a well-stirred solution of $NaBH_4$ (864 mg) in EtOH–H_2O (1: 1, 30 ml) during 5 min at 0—5°C under an N_2 atmosphere. After stirring at 0—5°C for 1 h and at room temperature for an additional 2 h, the mixture was poured into H_2O (150 ml) and extracted with $CHCl_3$ (15 ml×4). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue (1.17 g), which was subjected to vacuum distillation to give (*R*)-(+)-**45** (0.98 g) as a colorless oil, bp 85—88°C (1.0 mmHg). $[\alpha]_D^{20}$ +1.27° (*c*=18.07, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 3350, 2910, 1730 and 1365. ^1H NMR δ: 0.93 (d, J=5.5 Hz, 4-CH_3), 2.03 (s, –$OCOCH_3$), 2.78 (s, –OH), 3.60 (t, J=6.0 Hz, 1-H_2) and 4.12 (t, J=6.5 Hz, 6-H_2). *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.76; H, 10.61.

Preparation of (*R*)-(+)-1-Acetoxy-6-iodo-3-methylhexane ((*R*)-(+)-46) from (*R*)-(+)-6-Acetoxy-4-methylhexanol ((*R*)-(+)-45)——TsCl (1.50 g) was added to a solution of (*R*)-(+)-**45** (531 mg) in pyridine (4 ml) and the whole was allowed to stand at 5°C for 3 h. The mixture was poured into ice-water and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed successively with 1 N HCl, 10% $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. NaI (900 mg) was added to a solution of the resulting residue (976 mg) in dry acetone (9 ml) and the whole was stirred for 18 h at room temperature. The mixture was poured into ice-water and extracted with CH_2Cl_2 (10 ml×4). The extract was washed successively with 10% $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Vacuum distillation of the pale yellow oily residue (764 mg) gave (*R*)-(+)-**46** (699 mg) as a colorless oil, bp 110—114°C (3.6 mmHg). $[\alpha]_D^{20}$ +8.54° (*c*=50.24, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2900, 1725 and 1360. ^1H NMR δ: 0.93 (d, J=5.5 Hz, 3-CH_3) 2.04 (s, –$OCOCH_3$), 3.19 (t, J=7.0 Hz, 6-H_2) and 4.12 (t, J=6.5 Hz, 1-H_2). MS *m/z* (% rel. intensity): 284

(M^+, 1.5), 224 (M^+-AcOH, 12.2), 157 (M^+-I, 6.8), 97 ($C_7H_{13}^+$, 84.2), 83 ($C_6H_{11}^+$, 4.0), 69 ($C_5H_9^+$, 24.1), 55 ($C_4H_7^+$, 100.0) and 43 ($C_2H_3O^+$, 61.2).

Preparation of (*R*)-(+)-6-Iodo-3-methyl-1-(tetrahydropyranyloxy)hexane ((*R*)-(+)-47) from (*R*)-(+)-1-Acetoxy-6-iodo-3-methylhexane ((*R*)-(+)-46)——K_2CO_3 (173 mg) was added to a solution of (*R*)-(+)-**46** (647 mg) in MeOH–H_2O (4: 1, 3 ml) and the whole was stirred for 1 h at room temperature. The mixture was poured into H_2O and extracted with $CHCl_3$ (5 ml×4). The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. 2,3-Dihydropyran (268 mg) and PPTS (53 mg) was added to a solution of the resulting residue (513 mg) in dry CH_2Cl_2 (5 ml) and the whole was stirred at room temperature for 4 h. After removal of the solvent *in vacuo*, the residue was taken up in ether (50 ml) and the ethereal layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The pale yellow oily residue (624 mg) was subjected to vacuum distillation to afford (*R*)-(+)-**47** (604 mg) as a colorless oil, bp 115—118°C (4.5 mmHg). $[\alpha]_D^{20}$ +6.81° (c=17.81, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2900 and 1065. ^1H NMR δ: 0.92 (d, J=5.5 Hz, 3-CH_3), 3.16 (t, J=6.5 Hz, 6-H_2) and 4.54 (m, –O–CH–O–). MS m/z (% rel. intensity): 326 (M^+, 1.5), 325 (M^+-1, 9.8), 225 ($C_7H_{14}I^+$, 4.4), 199 (M^+-I, 7.2), 115 ($C_7H_{15}O^+$, 4.2), 97 ($C_7H_{13}^+$, 25.5), 85 ($C_5H_9O^+$, 100.0), 69 ($C_5H_9^+$, 12.9), 55 ($C_4H_7^+$, 51.5) and 41 ($C_3H_5^+$, 21.6).

Preparation of Bis(tetrahydropyranyloxy)acetone (31) from Diethyl Malonate (49)——Hexabutyldistanoxane (1.12 ml) was added to a stirred solution of glycerol (**48**)[18] (153 mg), derived from **49**, in dry THF (6.5 ml) under an N_2 atmosphere. A solution of Br_2 (0.11 ml) in dry THF (2.1 ml) was then added dropwise to the mixture at room temperature during 30 min and then the whole was heated at 40—45°C for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel column (5 g) with $CHCl_3$–MeOH mixtures of increasing MeOH content (1: 0, 50 ml; 49: 1, 100 ml; 19: 1, 50 ml and 0: 1, 50 ml), collecting 50 ml fractions. After concentration of the combined fr. 4—5 *in vacuo*, the oily residue (167 mg) was subjected to PLC ($CHCl_3$–MeOH 8: 2) to yield a colorless syrup (82 mg), which was treated with 2,3-dihydropyran (340 mg) and PPTS (65 mg) in dry CH_2Cl_2 (3 ml) in the usual manner. The reaction product (274 mg) was subjected to PLC (*n*-hexane–ether 1: 1) to give a colorless syrup (152 mg), which was recrystallized from *n*-hexane–ether to yield colorless needles (74 mg), mp 49—50°C. This substance was identical with compound **31** described above (mixed mp, IR and ^1H NMR). Treatment of [2-^{13}C]-glycerol (**48**) (436 mg), derived from [2-^{13}C]-**49**, in the same way as above gave [2-^{13}C]-**31** (394 mg). ^1H NMR δ: 4.38 (br d, $^2J_{H-1,C-2}$=$^2J_{H-3,C-2}$=4.0 Hz, 1-H_2, 3-H_2).

Wittig Reaction of Bis(tetrahydropyranyloxy)acetone (31) with (*R*)-(+)-(4-Methyl-6-(tetrahydropyranyloxy)hexane)-triphenylphosphonium Iodide ((*R*)-(+)-50) derived from (*R*)-(+)-6-Iodo-3-methyl-1-(tetrahydropyranyloxy)hexane ((*R*)-(+)-47)——Triphenylphosphine (178 mg) was added to a solution of (*R*)-(+)-**47** (222 mg) in dry benzene (2 ml) and the mixture was stirred at 70—80°C for 40 h under an N_2 atmosphere. After removal of the solvent by decantation, the resulting (*R*)-(+)-**50** (388 mg), a pale yellow syrup, was dissolved in dry THF (2 ml) and cooled to −20°C, then a solution of *n*-BuLi in hexane (0.43 ml, 1.6 M solution) was added during 5 min under an N_2 atmosphere. The whole was stirred at −15—0°C for a further 2 h and then at room temperature for 10 min. The mixture was cooled again to −20°C, then a solution of **31** (175 mg) in dry THF (1 ml) was added dropwise during 5 min. The whole was stirred at the same temperature for 30 min, then at room temperature for 1 h; finally it was stirred at 70—80°C for an additional 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$ (5 ml×4). The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue (566 mg) by PLC (*n*-hexane–ether 1: 1) gave (*R*)-(+)-9,10-dihydroxycitronellol tris(tetrahydropyranyl) ether ((*R*)-(+)-**51**) (140 mg) as a colorless oil, which was not distillable because of its lability. $[\alpha]_D^{20}$ +2.37° (c=7.59, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2920 and 1080. ^1H NMR δ: 0.93 (d, J=5.5 Hz, 4-H_3), 1.60 (m, 18H of pyran rings), 4.60 (m, –O–CH–O–×3) and 5.64 (br t, J=7.0 Hz, 7-H). *Anal.* Calcd for $C_{25}H_{44}O_6$: C, 68.15; H, 10.07. Found: C, 67.89; H, 10.29. Treatment of [2-^{13}C]-**31** (106 mg) with (*R*)-(+)-**50** (251 mg) in the same way as above gave (*R*)-(+)-[8-^{13}C]-**51** (86 mg).

Removal of the Tetrahydropyranyl Group from (*R*)-(+)-9,10-Dihydroxycitronellol Tris(tetrahydropyranyl) Ether ((*R*)-(+)-51)——PPTS (7 mg) was added to a solution (*R*)-(+)-**51** (132 mg) in EtOH (2.5 ml) and the mixture was stirred at 50°C for 9 h. After removal of the solvent *in vacuo*, the residue was purified by PLC (ether, 2 developments) to afford (*R*)-(+)-9,10-dihydroxycitronellol ((*R*)-(+)-**11**) (56 mg) as a colorless oil. $[\alpha]_D^{20}$ +3.38° (c=2.37, EtOH). This substance was not distillable. IR ν_{max}^{neat} cm^{-1}: 3260, 2900 and 1375. ^1H NMR δ: 0.90 (d, J=5.5 Hz, 4-H_3), 2.83 (br s, –OH×3), 3.64 (t, J=6.0 Hz, 1-H_2), 4.16 (br s, 10-H_2), 4.26 (br s, 9-H_2) and 5.49 (br t, J=7.5 Hz, 7-H). *Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.53; H, 10.86. Treatment of (*R*)-(+)-[8-^{13}C]-**51** (86 mg) with PPTS in the same way as above gave (*R*)-(+)-[8-^{13}C]-**11** (31 mg). ^1H NMR δ: 4.16 (br d, $^2J_{H-10,C-8}$=4.0 Hz, 10-H_2) and 4.26 (br d, $^2J_{H-9,C-8}$=4.0 Hz, 9-H_2). ^{13}C NMR (CD_3OD) δ: 60.93 (t, C_1), 40.58 (t, C_2), 30.24 (d, C_3), 19.89 (q, C_4), 38.23 (t, C_5), 25.69 (t, C_6), 129.62 (d, C_7), 138.94 (s, C_8), 58.80 (t, C_9) and 65.09 (t, C_{10}). High-resolution MS m/z: Calcd for $C_9{}^{13}CH_{20}O_3$ (M^+) 189.1446. Found: 189.1440.

Preparation of (*S*)-(−)-6-Acetoxy-4-methylhexanol ((*S*)-(−)-45) from (*S*)-(−)-Citronellyl Acetate ((*S*)-(−)-40)——Ozonolysis of (*S*)-(−)-**40** (500 mg) in the same way as for the preparation of (*R*)-(+)-**45** gave (*S*)-(−)-**45** (301 mg) as a colorless oil, bp 83—85°C (0.8 mmHg). $[\alpha]_D^{20}$ −1.41° (c=24.83, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found:

C, 61.99; H, 10.20.

Preparation of (*S*)-(−)-1-Acetoxy-6-iodo-3-methylhexane ((*S*)-(−)-46) from (*S*)-(−)-6-Acetoxy-4-methylhexanol ((*S*)-(−)-45)——Treatment of (*S*)-(−)-**45** (756 mg) in the same way as for the preparation of (*R*)-(+)-**46** gave (*S*)-(−)-**46** (982 mg) as a colorless oil, bp 99—103°C (0.7 mmHg). $[\alpha]_D^{20}$ −7.18° (c=10.23, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. MS m/z (% rel. intensity): 284 (M^+, 2.7), 224 (M^+-AcOH, 14.3), 157 (M^+-I, 11.2), 97 ($C_7H_{13}^+$, 81.1), 83 ($C_6H_{11}^+$, 22.3), 69 ($C_5H_9^+$, 27.0), 55 $C_4H_7^+$, 100.0) and 43 ($C_2H_3O^+$, 60.5).

Preparation of (*S*)-(−)-6-Iodo-3-methyl-1-(tetrahydropyranyloxy)hexane ((*S*)-(−)-47) from (*S*)-(−)-1-Acetoxy-6-iodo-3-methylhexane ((*S*)-(−)-46)——Treatment of (*S*)-(−)-**46** (741 mg) in the same way as for the preparation of (*R*)-(+)-**47** gave (*S*)-(−)-**47** (748 mg) as a colorless oil, bp 93—96°C (0.9 mmHg). $[\alpha]_D^{20}$ −5.97° (c=19.50, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. MS m/z (% rel. intensity): 326 (M^+, 2.0), 325 (M^+-1, 13.5), 225 ($C_7H_{14}I^+$, 6.6), 199 (M^+-I, 7.0), 115 ($C_7H_{15}O^+$, 12.9), 97 ($C_7H_{13}^+$, 42.6), 85 ($C_5H_9O^+$, 100.0), 69 ($C_5H_9^+$, 23.3), 55 ($C_4H_7^+$, 76.1) and 41 ($C_3H_5^+$, 34.3).

Wittig Reaction of Bis(tetrahydropyranyloxy)acetone (31) with (*S*)-(−)-(4-Methyl-6-(tetrahydropyranyloxy)hexane)-triphenylphosphonium Iodide ((*S*)-(−)-50) derived from (*S*)-(−)-6-Iodo-3-methyl-1-(tetrahydropyranyloxy)hexane ((*S*)-(−)-47)——Treatment of (*S*)-(−)-**50** (568 mg), derived from (*S*)-(−)-**47** (326 mg), with **31** (217 mg) in the same way as for the preparation of (*R*)-(+)-**51** gave (*S*)-(−)-9,10-dihydroxycitronellol tris(tetrahydropyranyl) ether ((*S*)-(−)-**51**) (157 mg) as a colorless oil, which was not distillable because of its lability. $[\alpha]_D^{20}$ −2.29° (c=8.73, $CHCl_3$). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_{25}H_{44}O_6$: C, 68.15; H, 10.07. Found: C, 68.25; H, 10.22. Treatment of (*S*)-(−)-**50** (675 mg) with [2-^{13}C]-**31** (286 mg) in the same way as above gave (*S*)-(−)-[8-^{13}C]-**51** (222 mg).

Removal of the Tetrahydropyranyl Group from (*S*)-(−)-9,10-Dihydroxycitronellol Tris(tetrahydropyranyl) Ether ((*S*)-(−)-51)——Treatment of (*S*)-(−)-**51** (151 mg) with PPTS (9 mg) in the same way as for the preparation of (*R*)-(+)-**11** gave (*S*)-(−)-9,10-dihydroxycitronellol ((*S*)-(−)-**11**) (61 mg) as a colorless oil. This substance was not distillable $[\alpha]_D^{20}$ −3.88° (c=2.54, EtOH). IR and ^1H NMR spectra: the same as for the (*R*)-enantiomer. *Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.90; H, 10.89. Treatment of (*S*)-(−)-[8-^{13}C]-**51** (222 mg) with PPTS in the same way as above gave (*S*)-(−)-[8-^{13}C]-**11** (83 mg). High-resolution MS m/z: Calcd for $C_9{}^{13}CH_{20}O_3$ (M^+) 189.1446. Found: 189.1449.

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